PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 403/04, 471/04, 491/04, 403/14, 405/14, A61K 31/50 — A1

(11) International Publication Number: **WO 99/46260**

(43) International Publication Date: 16 September 1999 (16.09.99)

(21) International Application Number: PCT/SE99/00276

(22) International Filing Date: 26 February 1999 (26.02.99)

(30) Priority Data:
9800836-0 13 March 1998 (13.03.98) SE

(71) Applicant *(for all designated States except US)*: ASTRA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KARABELAS, Kostas [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). LÖNN, Hans [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE). SJÖ, Peter [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NEW COMPOUNDS

(57) Abstract

The present invention relates to novel quinoxalinones which are inhibitors of protein kinase C. The invention further relates to formulations comprising said inhibitors of protein kinase C, use thereof in medical therapy and in the manufacture of a medicament for the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

NEW COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to novel quinoxalinones which are inhibitors of protein kinase C. The invention further relates to formulations comprising said inhibitors of protein kinase C, use thereof in medical therapy and in the manufacture of a medicament for the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

BACKGROUND OF THE INVENTION

Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine-specific protein kinases which play an important role in cellular growth control, regulation and differentiation.

Since the activation of PKC has been implicated in several human disease processes, including various forms of cancer, different forms of inflammatory and/or immunological disorders as well as some neurological disorders, inhibition of PKC could be of therapeutic value in treating these conditions.

Several classes of compounds have been identified as PKC inhibitors, e.g. isoquinoline sulphonamides, sphingosine and related sphingolipids, indolocarbazoles and bisindolylmaleimides.

Although PKC inhibitors are described in the prior art, there is a need for specific anti-inflammatory and immunosuppressive compounds which are suitable for oral administration, and for inhalation.

SUMMARY OF THE INVENTION

The present invention provides novel quinoxalinones which are PKC inhibitors.

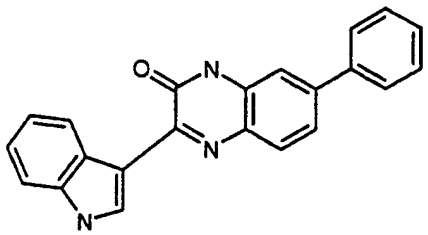
The present invention further provides novel quinoxalinones for use in medical therapy, and more particularly in the treatment of inflammatory, immunological, broncho-pulmonary, cardiovascular, oncological or CNS-degenerative disorders.

The present invention also provides use of the compounds of the present invention in the manufacture of a medicament for the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

Also provided by the present invention are pharmaceutical compositions comprising a compound according to the present invention, as active ingredient, together with a pharmaceutically acceptable adjuvant, diluent or carrier.

DETAILED DESCRIPTION OF THE INVENTION

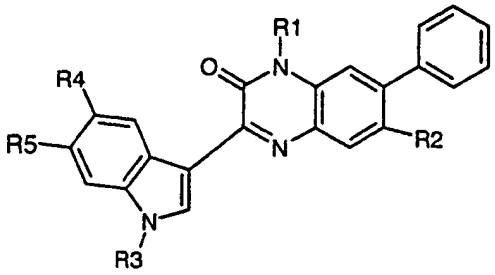
The present invention provides optionally substituted and/or annulated compounds of formula (I):



(I)

and salts thereof.

Specifically, the present invention provides compounds of formula (II):



(II)

wherein:

R1 is H, 2-amino-1-methyl-ethyl, 2-methylamino-ethyl, 2-amino-4-methyl-pentyl, piperidin-3-ylmethyl, piperidin-4-yl, 3-aminopropyl, 2-(2-amino-ethoxy)-ethyl or 5-amino-pentyl

R2 is H, halogen, or carboxyC_{1-6}alkyl

R3 is C_{1-6} alkyl, N,N-diethylacetamid-2-yl, 4-cyanobenzyl, tetrahydro-furan-2-ylmethyl, 3-amino-propyl or 3-amino-butyl

R4 and R5 are each independently H, halogen, benzyloxy or carboxyC_{1-6}alkyl

and salts thereof.

Preferred compounds are optionally substituted and/or annulated compounds comprising

i) 3-[1-(3-Amino-propyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one or

ii) 3-[1-(4-Amino-butyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one

and salts thereof.

More specifically, the present invention provides the compounds described in the Examples 1 to 155 hereto and salts thereof.

The most preferred compounds of the present invention are as follows:
1-(3-Amino-propyl)-3-(3-oxo-6-phenyl-3,4-dihydro-quinoxalin-2-yl)-1H-indole-5-carboxylic acid methyl ester acetic acid salt,

3-[1-(3-Amino-propyl)-6-benzyloxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-benzyloxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-bromo-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(4-Amino-butyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

and the corresponding free amines thereof and other pharmaceutically acceptable salts thereof.

Salts of the compounds according to the invention are preferably pharmaceutically acceptable salts. Other, non-pharmaceutically acceptable salts may be useful as intermediates e.g. in the preparation of pharmaceutically acceptable salts or other compound of the present invention.

Included within the scope of the present invention are all enol tautomers of compounds of the present invention as well as stereoisomers, pure and mixed racemates, and mixtures thereof.

Compounds of the present invention and pharmaceutically acceptable salts thereof, are useful because they demonstrate pharmacological activity. In particular they demonstrate activity as kinase inhibitors, especially PKC inhibitors, e.g. as is shown by their activity in the in vitro assays described in Granet, R.A. et al, Analyt. Biochem. 1987; 163, 458-463; Olsson, H. et al, Cell Signal 1989, 1, 405-410; Chakravarthy, B.R. et al, Analyt. Biochem. 1991, 196, 144-150 and Bergstrand, H et al, J. Pharm. Exp. Ther. 1992; 263(3), 1334-1346.

In appropriate cellular systems, compounds of the present invention and pharmaceutical acceptable salts thereof, can also reduce the generation of inflammatory mediators. For example, the compounds can inhibit oxygen radical generation and generation of pro-inflammatory cytokines in monocytes. The compounds are especially useful as inhibitors of one or more cytokines selected from IL-1β, TNF-α, GM-CSF or IL-8.

The compounds of the invention are indicated for use in medical therapy. More particularly, the compounds of the invention are indicated for use in the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders. Preferably for oral or topical treatment of inflammatory and/or immunological disorders, such as the oral or topical treatment of airway diseases involving inflammatory conditions, e.g. asthma, bronchitis or atopic diseases, e.g. rhinitis or atopic dermatitis; inflammatory bowel diseases, e.g. Crohn's disease or colitis; autoimmune diseases e.g. multiple sclerosis, diabetes, atherosclerosis, psoriasis, systemic lupus erythematosus or rheumatoid arthritis; malignant diseases, e.g. skin or lung cancer; HIV infections or AIDS; or for inhibiting rejection of organs/transplants.

The compounds of the invention are also indicated for use in the manufacture of a medicament for the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

The present invention is also directed to a method for the treatment of an inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative

disorder, wherein a therapeutically effective amount of a compound of the invention is administered to a mammal in the need of such treatment.

The dose of the compound to be administered will depend upon the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will preferably be in the range of from 0.1 mg/kg to 100 mg/kg.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, aerosols or dry powder formulations, e.g. formulations in the inhaler device known as the Turbuhaler® (trademark of Astra AB of Sweden), or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration, e.g. in the form of sterile parenteral solutions or suspensions, or by rectal administration, e.g. in the form of suppositories.

Compounds of the invention may be administered on their own or as a pharmaceutical composition comprising a compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 μm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (e.g. oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

Compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol, or an other polyol. Suitable carriers are sugars, e.g. lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol; a starch, e.g. potato starch, corn starch or amylopectin; a cellulose derivative; a binder, e.g. gelatine or polyvinylpyrrolidone, and/or a lubricant, e.g. magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for solutions containing the compound, the balance being sugar and a mixture of ethanol,

water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The term 'medical therapy' as used herein is intended to include prophylactic, diagnostic and therapeutic regimens carried out in vivo or ex vivo on humans or other mammals.

EXAMPLES

The following Examples are intended to illustrate, but in no way limit the scope of the invention.

All reactions were performed in dried glassware under Ar or N_2 unless otherwise noted. Tetrahydrofuran was distilled from sodium/benzophenone. Dimethyl formamide (DMF) was distilled from calcium hydride, or dried over molecular sieves. Other solvents and all commercial reagents were laboratory grade and used as received.

^1H - NMR spectra were recorded on a Varian XL-300, Varian Unity Inova 400 or a Varian Unity Inova 500 instrument. The central solvent peaks of chloroform-*d* (δ_H 7.27 ppm) and dimethyl sulphoxide-d_6 (δ_H 2.50 ppm) were used as internal references. Low-resolution mass spectra and accurate mass determinations were recorded on an Autospec-Q, Fisons Analytical, double focusing sector instrument equipped with a LSIMS interface. Low resolution mass spectra were also obtained on a Hewlett Packard 1100 LC-MS system equipped with APCI ionisation chamber.

DMSO is dimethylsulfoxide, MeOH is methanol and HOAc is acetic acid.

Example 1

3-(1-Ethyl-1H-indol-3-yl)-1-piperidin-3-ylmethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

Polymeric imidazolide carbamate (3g, 3.0 mmol, prepared as described by Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* 1995, *36*, 1589-1592, from a Wang resin purchased from Rapp Polymere GmbH, Tübingen, Germany, 1.1 mmol/g,) was heated in DMF (25 ml) containing 3-piperidine methanol (1.38g, 12 mmol) at 90 °C for 13h. The resin was filtered and washed (3 times, 30ml) DMF, CH_2Cl_2, MeOH, and dried in vacuum. Gel-phase ^{13}C-nmr ($CDCl_3$) showed formation of carbamate linked 3-piperidine methanol.

Oxalylchloride (25.9 ml, 0.3 mol) in CH_2Cl_2 (133ml) was added droppwise to DMSO in CH_2Cl_2 (133ml) during 30 min, at -78^{0}C. After additional 15 min s-collidine (79ml, 0.6 mmol) in CH_2Cl_2 (133ml) was added during 20 min, and 15 min later a part of the cool activated DMSO-solution (50 ml, approx. 30 mmol) was added to the dried carbamate linked 3-piperidine methanol resin (approx. 3 mmol), and the mixture was shaken over night at room temperature. The resin was filtered and washed (3 times, 50ml) CH_2Cl_2, THF-H2O-pyridine-6:2:1, THF, CH_2Cl_2, MeOH, and dried in vacuum. Gel-phase ^{13}C-nmr ($CDCl_3$) showed oxidation of the carbamate linked 3-piperidine methanol.

A solution of 1,2-phenylenediamine (276 mg, 2.55mmol) and sodium triacetoxy borohydride (540 mg, 2.55 mmol) in DMF-HOAc (10:1, 8.5 ml) was added to the oxidised resin bound product (850 mg, 0.81 mmol), and the mixture was shaken over night at room temperature. The resin was filtered and washed (3 times, 10ml) DMF, THF-H2O-NEt_3-6:2:1, DMF, CH_2Cl_2, MeOH, and dried in vacuum. Gel-phase ^{13}C-nmr ($CDCl_3$) showed formation of N-alkylated 1,2-diaminobenzene.

The N-alkyl-1,2-diaminobenzene resin (75mg, 0.058 mmol) and 1-ethylindole-3-glyoxylic acid (79 mg, 0.36 mmol) in DMSO (0.28 ml) was heated at 100 °C for 1 h. The resin was

filtered and washed (4 times, 1ml) DMF, CH_2Cl_2-MeCN-1:1, and reacted in CH_2Cl_2-MeCN-1:1(0.4 ml) with TFA-Me_2S-H_2O-95:5:5 (0.8 ml) for 0.5 h. Water (0.27 ml) was added, after 5 min the resin was filtered and washed twice with CH_2Cl_2-MeCN (1:1, 1 ml). The combined filtrate and washings were concentrated and coevaporated with MeCN and the residue was dried in vacuum to give the title product (26 mg, 90%), purity 63% (HPLC, 254 nm). LC/APCI-MS showed the title product being the major component with m/z 387 [MH+].

An analytically pure sample of the corresponding free amine was obtained by silica gel chromatography (CH_2Cl_2-MeOH-NEt_3-100:33:1).

^{1}H-NMR of the free amine (500 MHz, DMSO-d_6): δ 1.31 (1H, m), 1.32 (1H, m), 1.44 (3H, t, *J* 7.2 Hz), 1.62 (1H, m), 1.75 (1H, m), 2.05 (1H, m), 2.47 (1H, dd, *J* 10.0, 11.0 Hz), 2.50 (1H, m), 2.85 (1H, m), 2.87 (1H, m), 4.21 (1H, dd, *J* 13.6, 6.4 Hz), 4.34 (1H, dd, *J* 13.6, 8.3 Hz), 4.35 (2H, q, *J* 7.2 Hz), 7.26-7.32 (2H, m), 7.39 (1H, br t, *J* 7.4 Hz), 7.54 (1H, br t, *J* 7.7 Hz), 7.61 (1H, m), 7.62 (1H, m), 7.93 (1H, dd, *J* 7.9, 1.4 Hz),), 8.92 (1H, br d, *J* 7.7 Hz), 8.96 (1H, s).

Example 2

3-[1-(3-Amino-propyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

a) {1-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-1H-indol-3-yl}-oxo-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester

1-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-propyl]-1H-indol (1.00 g, 3.29 mmol) was dissolved in dichloromethane (10 ml) and cooled to 0°C. Oxalylchloride (0.28 ml, 3.29 mmol) was added and the reaction kept at 0°C for 30 minutes before the addition of N-hydroxysuccinimide (0.38 g, 3.29 mmol) followed by careful addition of pyridine (0.53 ml, 6.57 mmol).

After stirring the reaction for 1 hour at room temperature brine (5%, 10 ml) was added and the phases separated, the organic phase was washed with brine (5%, 2 x 10 ml), dried over Na_2SO_4 followed by removal of the solvent *in vacuo*. Crystallisation of the crude product from ethyl acetate - hexane yields the title product, 1.06 g (69%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.36 (2H, p, *J* 6.9 Hz), 2.93 (4H, s), 3.82 (2H, t, *J* 6.5 Hz), 4.29 (2H, t, *J* 7.5 Hz), 7.33-7.44 (3H, m), 7.70-7.75 (2H, m), 7.78-7.83 (2H, m), 8.32-8.36 (1H, m), 8.50 (1H, s).

FAB-MS: m/z 474 [MH+]

b) 2-{3-[3-(3-Oxo-8-phenyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-propyl}-isoindole-1,3-dione

1,2-Diamino-3-phenylbenzene (0.135 g, 0.57 mmol) and the product of step a) (0.250 g, 0.53 mmol) was dissolved in tetrahydrofuran (2.5 ml). Stirring overnight gives a yellow precipitate that was filtered off and washed with tetrahydrofuran/diethylether yielding the sub-title product (0.141 g, 51%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.16 (2H, p, *J* 6.9 Hz), 3.67 (2H, t, *J* 6.7 Hz), 4.43 (2H, t, *J* 7.3 Hz), 6.77 (1H, t, *J* 7.8 Hz), 6.95 (1H, dd, *J* 1.3, 7.5 Hz), 7.28-7.55 (8H, m), 7.70-7.76 (1H, m), 7.79-7.88 (4H, m), 8.27-8.34 (1H, m), 8.94 (1H, s), 9.97 (1H, s).

The product of step b) (0.142 g, 0.253 mmol) was suspended in tetrahydrofuran (1 ml) and aqueous methylamine (40%, 1 ml) was added. After stirring overnight the solvent was removed *in vacuo*. The residue was washed with water and treated with glacial acetic acid to obtain the title compound after freeze drying as a yellow solid (0.111 g, 99%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.90 (2H, q, *J* 6.7 Hz), 2.58 (2H, t, *J* 6.9 Hz), 4.35 (2H, t, *J* 7.1 Hz), 6.84 (1H, t, *J* 7.6 Hz), 7.18 (1H, t, *J* 8.1 Hz), 7.30 (1H, d, *J* 7.6 Hz), 7.35 (1H,

d, *J* 8.2 Hz), 7.49 (1H, t, *J* 8.2 Hz), 7.50-7,57 (4H, m), 7.62-7.67 (2H, m), 8.17 (1H, d, *J* 8.3 Hz), 8.96 (1H, s).

FAB-MS: m/z 395.1 [MH+].

The following examples were synthesised following the methods described above:

Example 3

1-(6-Amino-hexyl)-6,7-dichloro-3-[1-(3-methoxy-benzyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

FAB-MS: m/z 550 [MH+]

Example 4

1-(5-Amino-pentyl)-6,7-dichloro-3-[1-(3-methoxy-benzyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

FAB-MS: m/z 536 [MH+]

Example 5

1-(3-Hydroxymethyl-benzyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one

FAB-MS: m/z 410 [MH+]

Example 6

1-[3-(4-Hydroxy-phenyl)-propyl]-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one

FAB-MS: m/z 424 [MH+]

Example 7

3-(1H-Indol-3-yl)-6,7-dimethyl-1-(2-piperazin-1-yl-ethyl)-1H-quinoxalin-2-one bis trifluoroacetic acid salt

FAB-MS: m/z 402 [MH+]

Example 8

1-[2-(2-Amino-ethoxy)-ethyl]-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

FAB-MS: m/z 377 [MH+]

Example 9

1-(2-Amino-ethyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

FAB-MS: m/z 333 [MH+]

Example 10

1-(2-Amino-1-methyl-ethyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

FAB-MS: m/z 347 [MH+]

Example 11

1-(4-Amino-cyclohexyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

FAB-MS: m/z 387 [MH+]

Example 12

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-1H-pyrido[2,3-b]pyrazin-2-one acetic acid salt

FAB-MS: m/z 365 [MH+]

Example 13

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 392 [MH+]

Example 14

2-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-4H-pyrido[3,4-b]pyrazin-3-one acetic acid salt

FAB-MS: m/z 365 [MH+]

Example 15

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-7-trifluoromethyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 432 [MH+]

Example 16

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-1H-pyrido[2,3-b]pyrazin-2-one acetic acid salt

FAB-MS: m/z 347 [MH+]

Example 17

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 375 [MH+]

Example 18

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-6,7-dichloro-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 416 [MH+]

Example 19

2-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-4H-pyrido[3,4-b]pyrazin-3-one acetic acid salt

FAB-MS: m/z 348 [MH+]

Example 20

2-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-4H-pyrido[3,4-b]pyrazin-3-one acetic acid salt

FAB-MS: m/z 361 [MH+]

Example 21

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-7-trifluoromethyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 415 [MH+]

Example 22

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-7-nitro-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 392 [MH+]

Example 23

3-[5-(3-Aminomethyl-benzyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 501.6 [MH+]

Example 24

3-[5-(3-Amino-propyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 439.5 [MH+]

Example 25

3-[1-(3-Amino-propyl)-5-dibenzylamino-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 590.7 [MH+]

Example 26

3-[1-(3-Amino-propyl)-2-(4-chloro-phenyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 506.0 [MH+]

Example 27

3-[1-(3-Amino-propyl)-2-methyl-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 409.5 [MH+]

Example 28

1-(3-Amino-propyl)-3-(3-oxo-6-phenyl-3,4-dihydro-quinoxalin-2-yl)-1H-indole-5-carboxylic acid methyl ester acetic acid salt

FAB-MS: m/z 453.5 [MH+]

Example 29

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 440.5 [MH+]

Example 30

3-[1-(3-Amino-propyl)-5-methoxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 425.5 [MH+]

Example 31

3-[5-(3-Aminomethyl-benzyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 501.6 [MH+]

Example 32

3-[5-(3-Amino-propyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 439.5 [MH+]

Example 33

3-[1-(3-Amino-propyl)-5-dibenzylamino-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 590.7 [MH+]

Example 34

3-[1-(3-Amino-propyl)-2-methyl-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 409.5 [MH+]

Example 35

1-(3-Amino-propyl)-3-(3-oxo-8-phenyl-3,4-dihydro-quinoxalin-2-yl)-1H-indole-5-carboxylic acid methyl ester acetic acid salt

FAB-MS: m/z 453.5 [MH+]

Example 36

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 440.5 [MH+]

Example 37

3-[1-(3-Amino-propyl)-5-methoxy-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 425.5 [MH+]

Example 38

3-[1-(3-Amino-propyl)-6-benzyloxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 501.6 [MH+]

Example 39

3-[1-(3-Amino-propyl)-5-benzyloxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 501.6 [MH+]

Example 40

3-[1-(3-Amino-propyl)-5-bromo-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 473.0, 475.0 [MH+]

Example 41

3-[1-(3-Amino-propyl)-2-ethyl-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 423.5 [MH+]

Example 42

3-[1-(4-Amino-butyl)-2-benzyl-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 499.6 [MH+]

Example 43

3-[1-(6-Aminomethyl-pyridin-2-ylmethyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 458.5 [MH+]

Example 44

3-[1-(4-Aminomethyl-benzyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 457.6 [MH+]

Example 45

3-[1-(3-Aminomethyl-benzyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 457.6 [MH+]

Example 46

3-[1-(4-Amino-butyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 409.5 [MH+]

Example 47

3-[1-(3-Amino-propyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 395.5 [MH+]

Example 48

3-[1-(3-Amino-propyl)-6-benzyloxy-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 501.6 [MH+]

Example 49

3-[1-(3-Amino-propyl)-5-benzyloxy-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 501.6 [MH+]

Example 50

3-[1-(3-Amino-propyl)-5-bromo-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 473.0, 475.0 [MH+]

Example 51

3-[1-(3-Amino-propyl)-2-ethyl-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 423.5 [MH+]

Example 52

3-[1-(4-Amino-butyl)-2-benzyl-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 499.6 [MH+]

Example 53

3-[1-(4-Aminomethyl-benzyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 457.6 [MH+]

Example 54

3-[1-(3-Aminomethyl-benzyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 457.6 [MH+]

Example 55

3-[1-(4-Amino-butyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 409.5 [MH+]

Example 56

3-[1-(3-Amino-propyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

FAB-MS: m/z 395.5 [MH+]

Example 57

1-(2-Amino-1-methyl-ethyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 347 [MH+]

Example 58

2-{3-[4-(2-Amino-1-methyl-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 432 [MH+]

Example 59

4-{3-[4-(2-Amino-1-methyl-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 434 [MH+]

Example 60

1-(2-Amino-1-methyl-ethyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 403 [MH+]

Example 61

3-(1-Ethyl-1H-indol-3-yl)-1-(2-methylamino-ethyl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 347 [MH+]

Example 62

N,N-Diethyl-2-{3-[4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-acetamide trifluoroacetic acid salt

APCI-MS: 432 [MH+]

Example 63

4-{3-[4-(2-Methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 434 [MH+]

Example 64

1-(2-Methylamino-ethyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 403 [MH+]

Example 65

1-(2-Amino-4-methyl-pentyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 389 [MH+]

Example 66

2-{3-[4-(2-Amino-4-methyl-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 474 [MH+]

Example 67

4-{3-[4-(2-Amino-4-methyl-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 476 [MH+]

Example 68

1-(2-Amino-4-methyl-pentyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 445 [MH+]

3-(1-Ethyl-1H-indol-3-yl)-1-piperidin-3-ylmethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 387 [MH+]

Example 70

N,N-Diethyl-2-[3-(3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetamide trifluoroacetic acid salt

APCI-MS: 472 [MH+]

4-[3-(3-Oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

APCI-MS: 474 [MH+]

Example 72

1-Piperidin-3-ylmethyl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 443 [MH+]

Example 73

3-(1-Ethyl-1H-indol-3-yl)-1-piperidin-4-yl-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 373 [MH+]

Example 74

N,N-Diethyl-2-[3-(3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetamide trifluoroacetic acid salt

APCI-MS: 458 [MH+]

Example 75

4-[3-(3-Oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

APCI-MS: 460 [MH+]

Example 76

1-Piperidin-4-yl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 429 [MH+]

Example 77

1-(3-Amino-propyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 347 [MH+]

Example 78

2-{3-[4-(3-Amino-propyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 432 [MH+]

Example 79

4-{3-[4-(3-Amino-propyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 434 [MH+]

Example 80

1-(3-Amino-propyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 403 [MH+]

Example 81

1-[2-(2-Amino-ethoxy)-ethyl]-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 377 [MH+]

Example 82

2-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-yl)-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 462 [MH+]

Example 83

4-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-ylmethyl)-benzonitrile trifluoroacetic acid salt

APCI-MS: 464 [MH+]

Example 84

1-[2-(2-Amino-ethoxy)-ethyl]-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 433 [MH+]

Example 85

1-(5-Amino-pentyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 375 [MH+]

Example 86

2-{3-[4-(5-Amino-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 460 [MH+]

Example 87

4-{3-[4-(5-Amino-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 462 [MH+]

Example 88

1-(5-Amino-pentyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 431 [MH+]

Example 89

1-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 415, 417 [MH+]

Example 90

2-{3-[4-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 500, 502 [MH+]

Example 91

4-{3-[4-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 502, 504 [MH+]

Example 92

1-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 471, 473 [MH+]

Example 93

6,7-Dichloro-3-(1-ethyl-1H-indol-3-yl)-1-(2-methylamino-ethyl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 415, 417 [MH+]

Example 94

2-{3-[6,7-Dichloro-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 500, 502 [MH+]

Example 95

4-{3-[6,7-Dichloro-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 502, 504 [MH+]

Example 96

6,7-Dichloro-1-(2-methylamino-ethyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 471, 473 [MH+]

Example 97

1-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 457, 459 [MH+]

Example 98

2-{3-[4-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 542, 544 [MH+]

Example 99

4-{3-[4-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 544, 546 [MH+]

Example 100

1-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 513, 515 [MH+]

Example 101

6,7-Dichloro-3-(1-ethyl-1H-indol-3-yl)-1-piperidin-3-ylmethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 455, 457 [MH+]

Example 102

2-[3-(6,7-Dichloro-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 540, 542 [MH+]

Example 103

4-[3-(6,7-Dichloro-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

APCI-MS: 542, 544 [MH+]

Example 104

6,7-Dichloro-1-piperidin-3-ylmethyl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 511, 513 [MH+]

Example 105

6,7-Dichloro-3-(1-ethyl-1H-indol-3-yl)-1-piperidin-4-yl-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 441, 443 [MH+]

Example 106

2-[3-(6,7-Dichloro-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 526, 528 [MH+]

Example 107

4-[3-(6,7-Dichloro-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

APCI-MS: 528, 530 [MH+]

Example 108

6,7-Dichloro-1-piperidin-4-yl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 497, 499 [MH+]

Example 109

1-(3-Amino-propyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 415, 417 [MH+]

Example 110

2-{3-[4-(3-Amino-propyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 500, 502 [MH+]

Example 111

4-{3-[4-(3-Amino-propyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 502, 504 [MH+]

Example 112

1-(3-Amino-propyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 471, 473 [MH+]

Example 113

1-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 445, 447 [MH+]

Example 114

2-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-yl)-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 530, 532 [MH+]

Example 115

4-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-ylmethyl)-benzonitrile trifluoroacetic acid salt

APCI-MS: 532, 534 [MH+]

Example 116

1-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 501, 503 [MH+]

Example 117

1-(5-Amino-pentyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 443, 445 [MH+]

Example 118

2-{3-[4-(5-Amino-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

APCI-MS: 528, 530 [MH+]

Example 119

4-{3-[4-(5-Amino-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

APCI-MS: 530, 532 [MH+]

Example 120

1-(5-Amino-pentyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 499, 501 [MH+]

Example 121

4-(2-Amino-1-methyl-ethyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 405 [MH+]

Example 122

4-(2-Amino-1-methyl-ethyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 490 [MH+]

Example 123

4-(2-Amino-1-methyl-ethyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 492 [MH+]

Example 124

4-(2-Amino-1-methyl-ethyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 461 [MH+]

Example 125

2-(1-Ethyl-1H-indol-3-yl)-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 405 [MH+]

Example 126

2-(1-Diethylcarbamoylmethyl-1H-indol-3-yl)-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 490 [MH+]

Example 127

2-[1-(4-Cyano-benzyl)-1H-indol-3-yl]-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 492 [MH+]

Example 128

4-(2-Methylamino-ethyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 461 [MH+]

Example 129

4-(2-Amino-4-methyl-pentyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 447 [MH+]

Example 130

4-(2-Amino-4-methyl-pentyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 532 [MH+]

Example 131

4-(2-Amino-4-methyl-pentyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 534 [MH+]

Example 132

4-(2-Amino-4-methyl-pentyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 503 [MH+]

Example 133

2-(1-Ethyl-1H-indol-3-yl)-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 445 [MH+]

Example 134

2-(1-Diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 530 [MH+]

Example 135

2-[1-(4-Cyano-benzyl)-1H-indol-3-yl]-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 532 [MH+]

Example 136

3-Oxo-4-piperidin-3-ylmethyl-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 501 [MH+]

Example 137

2-(1-Ethyl-1H-indol-3-yl)-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 431 [MH+]

Example 138

2-(1-Diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 516 [MH+]

Example 139

2-[1-(4-Cyano-benzyl)-1H-indol-3-yl]-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 518 [MH+]

Example 140

3-Oxo-4-piperidin-4-yl-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 487 [MH+]

Example 141

4-(3-Amino-propyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 405 [MH+]

Example 142

4-(3-Amino-propyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 490 [MH+]

Example 143

4-(3-Amino-propyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 492 [MH+]

Example 144

4-(3-Amino-propyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 461 [MH+]

Example 145

4-[2-(2-Amino-ethoxy)-ethyl]-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 435 [MH+]

Example 146

4-[2-(2-Amino-ethoxy)-ethyl]-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 520 [MH+]

Example 147

4-[2-(2-Amino-ethoxy)-ethyl]-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 522 [MH+]

Example 148

4-[2-(2-Amino-ethoxy)-ethyl]-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 491 [MH+]

Example 149

4-(5-Amino-pentyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 433 [MH+]

Example 150

4-(5-Amino-pentyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 518 [MH+]

Example 151

4-(5-Amino-pentyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 520 [MH+]

Example 152

4-(5-Amino-pentyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

APCI-MS: 489 [MH+]

Example 153

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-6-methyl-1H-quinoxalin-2-one acetic acid salt

APCI-MS: 362 [MH+]

Example 154

1-(5-Amino-pentyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: 375 [MH+]

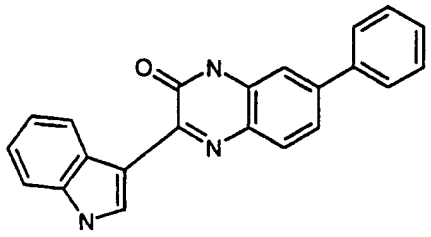
Example 155

1-[2-(2-Amino-ethoxy)-ethyl]-3-[1-(3-methoxy-benzyl)-1H-indol-3-yl]-1H-benzo[g]quinoxalin-2-one trifluoroacetic acid salt

APCI-MS: m/z 519 [MH+]

CLAIMS

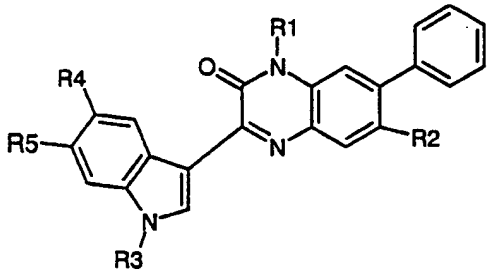
1. An optionally substituted and/or annulated compound of formula (I):



(I)

and salts thereof.

2. A compound according to claim 1, of formula (II):



(II)

wherein:

R1 is H, 2-amino-1-methyl-ethyl, 2-methylamino-ethyl, 2-amino-4-methyl-pentyl, piperidin-3-ylmethyl, piperidin-4-yl, 3-aminopropyl, 2-(2-amino-ethoxy)-ethyl or 5-amino-pentyl,

R2 is H, halogen, or carboxyC_{1-6}alkyl,

R3 is C_{1-6} alkyl, N,N-diethylacetamid-2-yl, 4-cyanobenzyl, tetrahydro-furan-2-ylmethyl, 3-amino-propyl or 3-amino-butyl,

R4 and R5 are each independently H, halogen, benzyloxy or carboxyC_{1-6}alkyl,

and salts thereof.

3. An optionally substituted and/or annulated compound according to claim 2, comprising

i) 3-[1-(3-Amino-propyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one or
ii) 3-[1-(4-Amino-butyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one

and salts thereof.

4. The compounds:

1-(3-Amino-propyl)-3-(3-oxo-6-phenyl-3,4-dihydro-quinoxalin-2-yl)-1H-indole-5-carboxylic acid methyl ester acetic acid salt,

3-[1-(3-Amino-propyl)-6-benzyloxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-benzyloxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

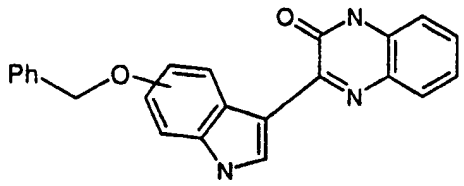
3-[1-(3-Amino-propyl)-5-bromo-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(4-Amino-butyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

and their free bases and other pharmaceutically acceptable salts thereof.

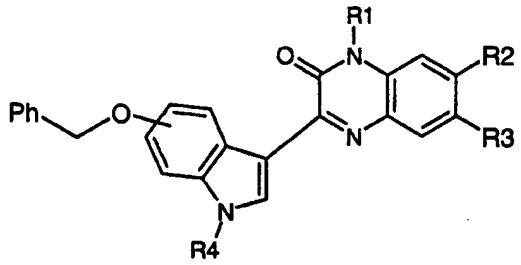
5. An optionally substituted and/or annulated compound of formula (III)



(III)

and salts thereof.

6. A compound according to claim 5, of formula (IV)



(IV)

wherein:

R1 is H, 2-amino-1-methyl-ethyl, 2-methylamino-ethyl, 2-amino-4-methyl-pentyl, piperidin-3-ylmethyl, piperidin-4-yl, 3-aminopropyl, 2-(2-amino-ethoxy)-ethyl or 5-amino-pentyl,

R2 is H, halogen, or carboxyC_{1-6}alkyl,

R3 is H, halogen, phenyl or carboxyC_{1-6}alkyl,

R4 is C_{1-6} alkyl, N,N-diethylacetamid-2-yl, 4-cyanobenzyl, tetrahydro-furan-2-ylmethyl,

3-amino-propyl or 3-amino-butyl,

and salts thereof.

7. The compounds:

3-(1-Ethyl-1H-indol-3-yl)-1-piperidin-3-ylmethyl-1H-quinoxalin-2-one trifluoroacetic acid salt,

3-[1-(3-Amino-propyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

1-(6-Amino-hexyl)-6,7-dichloro-3-[1-(3-methoxy-benzyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt,

1-(5-Amino-pentyl)-6,7-dichloro-3-[1-(3-methoxy-benzyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt,

1-(3-Hydroxymethyl-benzyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one,

1-[3-(4-Hydroxy-phenyl)-propyl]-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one,

3-(1H-Indol-3-yl)-6,7-dimethyl-1-(2-piperazin-1-yl-ethyl)-1H-quinoxalin-2-one bis trifluoroacetic acid salt,

1-[2-(2-Amino-ethoxy)-ethyl]-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt,

1-(2-Amino-ethyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt,

1-(2-Amino-1-methyl-ethyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt,

1-(4-Amino-cyclohexyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt,

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-1H-pyrido[2,3-b]pyrazin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-one acetic acid salt,

2-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-4H-pyrido[3,4-b]pyrazin-3-one acetic acid salt,

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-7-trifluoromethyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-1H-pyrido[2,3-b]pyrazin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-6,7-dimethyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-6,7-dichloro-1H-quinoxalin-2-one acetic acid salt,

2-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-4H-pyrido[3,4-b]pyrazin-3-one acetic acid salt,

2-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-4H-pyrido[3,4-b]pyrazin-3-one acetic acid salt,

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-7-trifluoromethyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-7-nitro-1H-quinoxalin-2-one acetic acid salt,

3-[5-(3-Aminomethyl-benzyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[5-(3-Amino-propyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-dibenzylamino-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-2-(4-chloro-phenyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-2-methyl-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-methoxy-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[5-(3-Aminomethyl-benzyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[5-(3-Amino-propyl)-5H-[1,3]dioxolo[4,5-f]indol-7-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-dibenzylamino-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-2-methyl-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

1-(3-Amino-propyl)-3-(3-oxo-8-phenyl-3,4-dihydro-quinoxalin-2-yl)-1H-indole-5-carboxylic acid methyl ester acetic acid salt,

3-[1-(3-Amino-propyl)-6-nitro-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-methoxy-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-2-ethyl-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(4-Amino-butyl)-2-benzyl-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(6-Aminomethyl-pyridin-2-ylmethyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(4-Aminomethyl-benzyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Aminomethyl-benzyl)-1H-indol-3-yl]-7-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-6-benzyloxy-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-benzyloxy-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-5-bromo-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt,

3-[1-(3-Amino-propyl)-2-ethyl-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

3-[1-(4-Amino-butyl)-2-benzyl-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

3-[1-(4-Aminomethyl-benzyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

3-[1-(3-Aminomethyl-benzyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

3-[1-(4-Amino-butyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

3-[1-(3-Amino-propyl)-1H-indol-3-yl]-5-phenyl-1H-quinoxalin-2-one acetic acid salt

1-(2-Amino-1-methyl-ethyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(2-Amino-1-methyl-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(2-Amino-1-methyl-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(2-Amino-1-methyl-ethyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

3-(1-Ethyl-1H-indol-3-yl)-1-(2-methylamino-ethyl)-1H-quinoxalin-2-one trifluoroacetic acid salt

N,N-Diethyl-2-{3-[4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-acetamide trifluoroacetic acid salt

4-{3-[4-(2-Methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(2-Methylamino-ethyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-(2-Amino-4-methyl-pentyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(2-Amino-4-methyl-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(2-Amino-4-methyl-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(2-Amino-4-methyl-pentyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

3-(1-Ethyl-1H-indol-3-yl)-1-piperidin-3-ylmethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

N,N-Diethyl-2-[3-(3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetamide trifluoroacetic acid salt

4-[3-(3-Oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

1-Piperidin-3-ylmethyl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

3-(1-Ethyl-1H-indol-3-yl)-1-piperidin-4-yl-1H-quinoxalin-2-one trifluoroacetic acid salt

N,N-Diethyl-2-[3-(3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-acetamide trifluoroacetic acid salt

4-[3-(3-Oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

1-Piperidin-4-yl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-(3-Amino-propyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(3-Amino-propyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(3-Amino-propyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(3-Amino-propyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-[2-(2-Amino-ethoxy)-ethyl]-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-yl)-N,N-diethyl-acetamide trifluoroacetic acid salt

4-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-ylmethyl)-benzonitrile trifluoroacetic acid salt

1-[2-(2-Amino-ethoxy)-ethyl]-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-(5-Amino-pentyl)-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(5-Amino-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(5-Amino-pentyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(5-Amino-pentyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(2-Amino-1-methyl-ethyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

6,7-Dichloro-3-(1-ethyl-1H-indol-3-yl)-1-(2-methylamino-ethyl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[6,7-Dichloro-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[6,7-Dichloro-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

6,7-Dichloro-1-(2-methylamino-ethyl)-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(2-Amino-4-methyl-pentyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

6,7-Dichloro-3-(1-ethyl-1H-indol-3-yl)-1-piperidin-3-ylmethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

2-[3-(6,7-Dichloro-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-N,N-diethyl-acetamide trifluoroacetic acid salt

4-[3-(6,7-Dichloro-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

6,7-Dichloro-1-piperidin-3-ylmethyl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

6,7-Dichloro-3-(1-ethyl-1H-indol-3-yl)-1-piperidin-4-yl-1H-quinoxalin-2-one trifluoroacetic acid salt

2-[3-(6,7-Dichloro-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-yl]-N,N-diethyl-acetamide trifluoroacetic acid salt

4-[3-(6,7-Dichloro-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxalin-2-yl)-indol-1-ylmethyl]-benzonitrile trifluoroacetic acid salt

6,7-Dichloro-1-piperidin-4-yl-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-(3-Amino-propyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(3-Amino-propyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(3-Amino-propyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(3-Amino-propyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-yl)-N,N-diethyl-acetamide trifluoroacetic acid salt

4-(3-{4-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl}-indol-1-ylmethyl)-benzonitrile trifluoroacetic acid salt

1-[2-(2-Amino-ethoxy)-ethyl]-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

1-(5-Amino-pentyl)-6,7-dichloro-3-(1-ethyl-1H-indol-3-yl)-1H-quinoxalin-2-one trifluoroacetic acid salt

2-{3-[4-(5-Amino-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-yl}-N,N-diethyl-acetamide trifluoroacetic acid salt

4-{3-[4-(5-Amino-pentyl)-6,7-dichloro-3-oxo-3,4-dihydro-quinoxalin-2-yl]-indol-1-ylmethyl}-benzonitrile trifluoroacetic acid salt

1-(5-Amino-pentyl)-6,7-dichloro-3-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-1H-quinoxalin-2-one trifluoroacetic acid salt

4-(2-Amino-1-methyl-ethyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Amino-1-methyl-ethyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Amino-1-methyl-ethyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Amino-1-methyl-ethyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-(1-Ethyl-1H-indol-3-yl)-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-(1-Diethylcarbamoylmethyl-1H-indol-3-yl)-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-[1-(4-Cyano-benzyl)-1H-indol-3-yl]-4-(2-methylamino-ethyl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Methylamino-ethyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Amino-4-methyl-pentyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Amino-4-methyl-pentyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Amino-4-methyl-pentyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(2-Amino-4-methyl-pentyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-(1-Ethyl-1H-indol-3-yl)-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-(1-Diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-[1-(4-Cyano-benzyl)-1H-indol-3-yl]-3-oxo-4-piperidin-3-ylmethyl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

3-Oxo-4-piperidin-3-ylmethyl-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-(1-Ethyl-1H-indol-3-yl)-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-(1-Diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

2-[1-(4-Cyano-benzyl)-1H-indol-3-yl]-3-oxo-4-piperidin-4-yl-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

3-Oxo-4-piperidin-4-yl-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(3-Amino-propyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(3-Amino-propyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(3-Amino-propyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(3-Amino-propyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-[2-(2-Amino-ethoxy)-ethyl]-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-[2-(2-Amino-ethoxy)-ethyl]-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-[2-(2-Amino-ethoxy)-ethyl]-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-[2-(2-Amino-ethoxy)-ethyl]-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(5-Amino-pentyl)-2-(1-ethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(5-Amino-pentyl)-2-(1-diethylcarbamoylmethyl-1H-indol-3-yl)-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(5-Amino-pentyl)-2-[1-(4-cyano-benzyl)-1H-indol-3-yl]-3-oxo-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

4-(5-Amino-pentyl)-3-oxo-2-[1-(tetrahydro-furan-2-ylmethyl)-1H-indol-3-yl]-3,4-dihydro-quinoxaline-6-carboxylic acid methyl ester trifluoroacetic acid salt

3-[1-(3-Amino-propyl)-7-ethyl-1H-indol-3-yl]-6-methyl-1H-quinoxalin-2-one acetic acid salt

1-(5-Amino-pentyl)-3-(1H-indol-3-yl)-6,7-dimethyl-1H-quinoxalin-2-one trifluoroacetic acid salt

1-[2-(2-Amino-ethoxy)-ethyl]-3-[1-(3-methoxy-benzyl)-1H-indol-3-yl]-1H-benzo[g]quinoxalin-2-one trifluoroacetic acid salt,

and their free bases and other pharmaceutically acceptable salts thereof

8. A pharmaceutical composition wherein the active ingredient is a compound according to any one of claims 1 to 7 together with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A compound according to any one of claims 1 to 7, for use in medical therapy.

10. The compound according to claim 9, wherein the medical therapy is the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

11. Use of a compound according to any one of claims 1 to 7 in the manufacture of a medicament for the treatment of inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders.

12. A method for treatment of an inflammatory, immunological, bronchopulmonary, cardiovascular, oncological or CNS-degenerative disorders, wherein a therapeutically effective amount of a compound according to any one of claims 1 to 7 is administered to a mammal in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00276

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 403/04, C07D 471/04, C07D 491/04, C07D 403/14, C07D 405/14, A61K 31/50
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9813368 A1 (ASTRA AKTIEBOLAG), 2 April 1998 (02.04.98)	2
X	example 7,11,34,49,67,72,84 and 89 -- --------	6

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 1999	17 -07- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00276

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☒ Claims Nos.: 1,3-5,7-11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please see extra sheet

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please see extra sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

The wording "optionally substituted and/or annulated" in claims 1, 3 and 5 is not clear and concise, cf. Article 6. These claims have therefore not been searched.

No common distinctive feature such as a common structure is given for the compounds according to claims 4 and 7. Due to the lack of such a feature, these claims state a separate invention for each compound given, cf. "requirements of unity of invention". No invitation to pay additional fees has been made as that would have meant more than 150 fees. Thus, claims 4, 7 and 8-11 have not been searched.

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship or interaction can be appreciated to be present so as to form a single general inventive concept.

Invention 1. Claim 2 (compound II)

Invention 2. Claim 6 (compound IV)

According to PCT Rule 13.2, the requirement of unity of invention is fulfilled only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The special technical feature shall also define a contribution which the claimed invention considered as a whole, makes over the prior art.

The special technical feature of each invention is a compound of formula II or IV respectively. No significant structural element over the prior art is shared by compound II and compound IV.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/06/99

International application No.
PCT/SE 99/00276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9813368 A1	02/04/98	AU 4477597 A	17/04/98
		SE 9603505 D	00/00/00
		SE 9702747 D	00/00/00

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☑ FADED TEXT OR DRAWING
- ☑ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☑ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 417/06, 209/10 // (C07D 417/06, 277:00, 209:00)

A2

(11) International Publication Number: WO 99/50268

(43) International Publication Date: 7 October 1999 (07.10.99)

(21) International Application Number: PCT/US99/07116

(22) International Filing Date: 31 March 1999 (31.03.99)

(30) Priority Data:
60/080,143 31 March 1998 (31.03.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/080,143 (CIP)
Filed on 31 March 1998 (31.03.98)

(71) Applicant *(for all designated States except US)*: THE INSTITUTES FOR PHARMACEUTICAL DISCOVERY, INC. [US/US]; 23 Business Park Drive, Branford, CT 06405 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JONES, Michael, L. [US/US]; 3710 Stoney Creek Road, Chapel Hill, NC 27514 (US). GUNN, David [US/US]; 40 Wood Street, Hamden, CT 06517 (US). JONES, John, Howard [US/US]; 3893 Main Street, Stratford, CT 06497 (US). VAN ZANDT, Michael, C. [US/US]; 56 Barker Hill Drive, Guilford, CT 06437 (US).

(74) Agent: SARUSSI, Steven, J.; McDonnell Boehnen Hulbert & Berghoff, Suite 3200, 300 South Wacker Drive, Chicago, IL 60606 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: SUBSTITUTED INDOLEALKANOIC ACIDS

(57) Abstract

Disclosed are substituted indolealkanoic acids useful in the treatment of chronic complications arising from diabetes mellitus. Also disclosed are pharmaceutical compositions containing the compounds and methods of treatment employing the compounds, as well as methods for their synthesis.

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

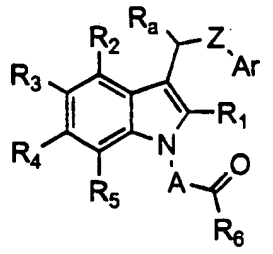
Inhibition. Porte, D. (ed), Biomedical Information Corp., New York, NY. Mc Graw Hill **1987**; (d) Petrash, J. M., Tarle, I., Wilson, D. K. Quiocho. F. A. Perspectives in Diabetes, *Aldose Reductase Catalysis and Crystalography: Insights From Recent Advances in Enzyme Structure and Function*, Diabetes, **1994**, *43*, 955; (e) Aotsuka, T.; Abe, N.; Fukushima, K.; Ashizawa, N.and Yoshida, M., *Bioorg. & Med. Chem. Letters*, **1997**, *7*, 1677, (f) , T., Nagaki, Y.; Ishii, A.; Konishi, Y.; Yago, H; Seishi, S.; Okukado, N.; Okamoto, K., *J. Med. Chem.*, **1997**, *40*, 684; (g) Ashizawa, N.; Yoshida, M.; Sugiyama, Y.; Akaike, N.; Ohbayashi, S.; Aotsuka, T.; Abe, N.; Fukushima, K.; Matsuura, A, *Jpn. J. Pharmacol*. **1997**, *73*, 133; (h) Kador, P. F.; Sharpless, N. E., *Molecular Pharmacology*, **1983**, *24*, 521; (I) Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E., *J. Med. Chem*. **1985**, 28 (7), 841; (j) Hotta, N., *Biomed. & Pharmacother*. **1995**, *5*, 232; (k) Mylar, B.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, F. D.; Siegel, T. W.; Singleton, D. H., *J. Med. Chem*. **1991**, *34*, 108; (l) Dvornik, D. *Croatica Chemica Acta* **1996**, *69* (2), 613.

Previously described aldose reductase inhibitors most closely related to the present invention include those sighted in: (a) U.S Pat. No. 5,700,819: *2-Substituted benzothiazole derivatives useful in the treatment of diabetic complications*, (b) U.S Pat. No. 4,868,301: *Processes and intermediates for the preparation of oxophthalazinyl acetic acids having*

benzothiazole or other heterocyclic side chains, (c) U.S Pat. No. 5,330,997: *1H-indazole-3-acetic acids as aldose reductase inhibitors*, and (d) U.S Pat. No. 5,236,945: *1H-indazole-3-acetic acids as aldose reductase inhibitors*. Although many aldose reductase inhibitors have been extensively developed, none have demonstrated sufficient efficacy in human clinical trials without significant undesirable side effects. Thus no aldose reductase inhibitors are currently available as approved therapeutic agents in the United States; and consequently, there is still a significant need for new, efficacious and safe medications for the treatment of diabetic complications.

Summary of the Invention:

This invention provides compounds that interact with and inhibit aldose reductase. Thus, in a broad aspect, the invention provides compounds of Formula I:



I

or pharmaceutically acceptable salts thereof wherein

A is a C_1-C_4 alkylene group optionally substituted with C_1-C_2 alkyl or mono- or disubstituted with halogen, preferably fluoro or chloro;

Z is a bond, O, S, C(O)NH, or C_1-C_3 alkylene optionally substituted with C_1-C_2 alkyl;

R_1 is hydrogen, alkyl having 1-6 carbon atoms, halogen, 2-, 3-, or 4-pyridyl, or phenyl, where the phenyl or pyridyl is optionally substituted with up to three groups selected from halogen, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, nitro, amino, or mono- or di(C_1-C_6)alkylamino;

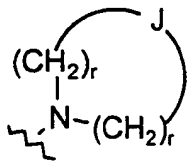
R_2, R_3, R_4 and R_5 are each independently

hydrogen, halogen, nitro, or an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens);

OR_7, SR_7, $S(O)R_7$, $S(O)_2(R_7)_2$, $C(O)N(R_7)_2$, or $N(R_7)_2$, wherein each R_7 is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

a group of the formula



where

J is a bond, CH_2, oxygen, or nitrogen; and

each r is independently 2 or 3;

R_6 is hydroxy or a prodrug group;

R_a is hydrogen, C_1-C_6 alkyl, fluoro, or trifluoromethyl; and

Ar represents aryl or heteroaryl, each of which is optionally substituted with up to five groups.

In another aspect, the invention provides methods for preparing such compounds.

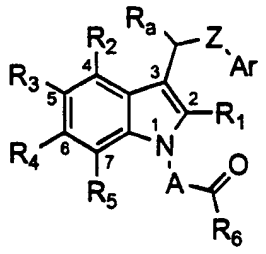
The compounds of the invention inhibit aldose reductase. Since aldose reductase is critical to the production of high levels of sorbitol in individuals with diabetes, inhibitors of aldose reductase are useful in preventing and/or treating various complications associated with diabetes. The compounds of the invention are therefore effective for the treatment of diabetic complications as a result of their ability to inhibit aldose reductase.

Thus, in another aspect, the invention provides methods for treating and/or preventing chronic complications associated with diabetes mellitus, including, for example, diabetic cataracts, retinopathy, nephropathy, and neuropathy.

In still another aspect, the invention provides pharmaceutical compositions containing compounds of Formula I.

Detailed Description of the Invention

The numbering system for the compounds of Formula I is as follows:



I

As noted above, the invention provides novel substituted indole alkanoic acids useful in treating and/or preventing complications associated with or arising from elevated levels of glucose in individuals suffering from diabetes mellitus. These compounds are represented by Formula I above.

In compounds of Formula I, the aryl and heteroaryl groups represented by Ar include:

a phenyl group optionally substituted with up to 5 groups independently selected from halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR_7, SR_7, $S(O)R_7$, $S(O)_2R_7$ or $N(R_7)_2$ wherein R_7 is hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, or the phenyl group may be condensed with

benzo where the benzo is optionally substituted with one or two of halogen, cyano, nitro, trifluoromethyl, perfluoroethyl, trifluoroacetyl, or (C_1-C_6)alkanoyl, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, trifluoromethoxy, trifluoromethylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl;

a heterocyclic 5-membered ring having one nitrogen, oxygen or sulfur, two nitrogens one of which may be replaced by oxygen or sulfur, or three nitrogens one of which may be replaced by oxygen or sulfur, said heterocyclic 5-membered ring substituted by one or two fluoro, chloro, (C_1-C_6)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thienyl, said phenyl or benzo optionally substituted by one of iodo, cyano, nitro, perfluoroethyl, trifluoroacetyl, or (C_1-C_6)alkanoyl, one or two of fluoro, chloro, bromo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, trifluoromethoxy, trifluoromethylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl or trifluoromethyl, or two fluoro or two trifluoromethyl with one hydroxy or one (C_1-C_6)alkoxy, or one or, preferably, two fluoro and one trifluoromethyl, or three fluoro, said pyridyl, furyl or thienyl optionally substituted in the 3-position by fluoro, chloro, bromo, (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

a heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur, said heterocyclic 6-membered ring substituted by one or two (C_1-C_6)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thienyl, said phenyl or benzo optionally substituted by one of iodo or trifluoromethylthio, or one or two of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, or trifluoromethyl, and said pyridyl, furyl or thienyl optionally substituted in the 3-position by fluoro, chloro, (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

said benzo-condensed heterocyclic 5-membered or 6-membered rings optionally substituted in the heterocyclic 5-membered or 6-membered ring by one of fluoro, chloro, bromo, methoxy, or trifluoromethyl;

oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms, with thiophene or with furane, each optionally substituted by one of fluoro, chloro, bromo, trifluoromethyl, methylthio or methylsulfinyl;

imidazolopyridine or triazolopyridine optionally substituted by one of trifluoromethyl, trifluoromethylthio, bromo, or (C_1-C_6)alkoxy, or two of fluoro or chloro;

thienothiophene or thienofuran optionally substituted by one of fluoro, chloro or trifluoromethyl; thienotriazole optionally substituted by one of chloro or trifluoromethyl;

naphthothiazole; naphthoxazole; or thienoisothiazole.

More specific compounds of the invention are those of Formula I wherein Ar is optionally substituted benzothiazolyl, benzoxazolyl, isoquinolyl, benzothiophen-yl, benzofuran-yl or benzimidazolyl, or substituted oxadiazolyl or indolyl. Other more specific compounds are of Formula I those wherein R_a is trifluoromethyl, Z is a covalent bond or CH_2, R_6 is hydroxy, and each of R_2-R_5 are independently hydrogen, halogen, more preferably bromo or chloro, C_1-C_2 alkyl, phenoxy, benzyloxy, or C_1-C_2 alkoxy, and R_1 is hydrogen or methyl.

Preferred compounds of the invention are those wherein Z is a covalent bond, R_6 is hydroxy, Ar is optionally substituted benzothiazol-2-yl, benzothiazol-5-yl, benzoisothiazol-3-yl, benzoxazol-2-yl, 2-quinolyl, 2-quinoxalyl, oxazolo[4,5-b]pyridine-2-yl, benzothiophen-2-yl, benzofuran-2-yl, or thazolo[4,5-pyridine-2-y, thieno[2,3-b]pyridine2-yl, imidazo[1,5-a]pyridine-2-yl, or indol-2-yl, or substituted 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, isothiazol-5-yl, isothiazol-4-yl, 1,3,4-oxadiazol-5-yl, 1,2,5-thiadiazol-3-yl, oxazol-2-yl, thiazol-2-yl, or thiazol-4-yl, R_2-R_5 are

independently hydrogen, halogen, more preferably bromo or chloro, C_1-C_2 alkyl, phenoxy, benzyloxy or phenyl where each phenyl portion is optionally substituted with C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, hydroxy, amino or mono- or di (C_1-C_6) alkylamino R_a is hydrogen,fluro or C_1-C_2 alkyl, and R_1 is hydrogen or methyl.

Other preferred compounds are those wherein the methylene bridge connecting the indolyl group with Ar is located alpha with respect to a nitrogen atom in Ar, e.g. wherein Ar is benzoxazol-2-yl or 1,2,4-oxadiazol-3-yl mentioned above.

Other more specific compounds of the invention are those wherein Z is a covalent bond, R_6 is hydroxy, R_a is hydrogen, Ar is optionally 4,5,6 or 7 benzo-substituted benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, or indolyl, or Ar is 2-benzothiazolyl substituted on benzo by one trifluoroacetyl or trifluoromethylthio, or one or two of fluoro chloro, bromo, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or one or, preferably, two fluoro and one trifluoromethyl, or two fluoro or two trifluoromethyl with one methoxy, or three fluoro, or by 6,7-benzo, and those wherein one of R_2 and R_3 is hydrogen, fluoro, chloro, bromo or methyl, and one of R_4 and R_5 is hydrogen, or chloro, bromo, methyl, isopropyl, methoxy, nitro or trifluoromethyl; or R_3 and R_4 is 5, 6-difluoro, R_a is hydrogen; and those wherein Ar is optionally substituted benzothiazol-2-

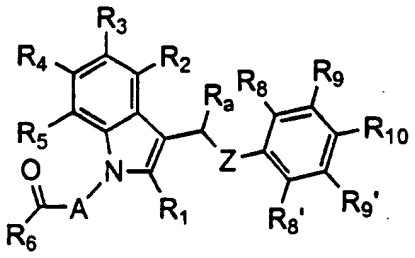
yl or quinoxalyl and R_3 and R_4 are each chloro, and R_1 is hydrogen or methyl.

Further more specific compounds are those wherein Z is a covalent bond, R_6 is hydroxy, Ar is optionally substituted benzothiazol-2-yl, R_3 and R_4 are hydrogen, and R_5 is methyl; those wherein Z is a covalent bond, R_6 is hydroxy, R_3, R_4 and R_5 are hydrogen, chloro, fluoro, bromo or C_1-C_2 alkyl, R_a is hydrogen, and Ar is optionally 4,5,6 or 7 benzosubstituted benzothiazolyl-2-trifluoromethyl, benzoxazolyl-2-trifluoromethyl, benzimidazolyl-2-trifluoromethyl, benzofuran-2-trifluoromethyl, benzofuran-3-trifluoromethyl, benzothiophen-2-trifluoromethyl, benzothiophen-3-trifluoromethyl, indolyl-2-trifluoromethyl, or indolyl-3-trifluoromethyl; and those wherein Z is CH_2, R_6 is hydroxy, Ar is optionally substituted benzothiazol-2-yl, benzothiazol-5-yl, benzoisothiazol-3-yl, benzoxazol-2-yl, 2-quinolyl, 2-quinoxalyl, oxazolo[4,5-b]pyridine-2-yl, or thiazolo[4,5-b]pyridine-2-yl, or substituted 1,2,4- oxadiazol3-yl, 1,2,4-oxadiazol-5-yl, isothiazol-5-yl, isothiazol4-yl, 1,3,4-oxadiazol-5-yl, 1,2,5-thiadiazol-3-yl, oxazol-2-yl, thiazol-2-yl, or thiazol-4-yl, and R_3, R_4 and R_5 are independently hydrogen, chloro, fluoro, bromo, C_1-C_2 alkyl, or trifluoromethyl, and R_a is hydrogen.

Generally, R_1 in the specific compounds described above is hydrogen, halogen, preferably chloro or fluoro, C_1-C_6 alkyl, or phenyl optionally substituted with with up to three groups

independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino. Preferred R_1 groups are hydrogen and methyl.

Preferred compounds of the invention include those where Ar in Formula I is substituted phenyl, i.e., compounds of Formula II:



II

wherein

A is a C_1-C_4 alkylene group optionally substituted with C_1-C_2 alkyl;

Z is a bond, or C_1-C_3 alkylene optionally substituted with C_1-C_2 alkyl;

R_a is hydrogen, C_1-C_6 alkyl, chloro, bromo, fluoro, or trifluoromethyl;

R_1 is hydrogen, C_1-C_6 alkyl, fluoro, or phenyl optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2, R_3, R_4 and R_5 are each independently

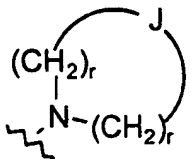
hydrogen, halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens),

nitro, OR_7, SR_7, $S(O)R_7$, $S(O)_2N(R_7)_2$, $C(O)N(R_7)_2$, or $N(R_7)_2$, wherein each R_7 is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

a group of the formula



where

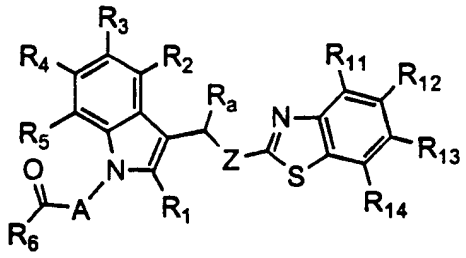
J is a bond, CH_2, oxygen, or nitrogen; and

each r is independently 2, or 3;

R_6 is hydrogen, an alkoxy group of 1-6 carbon atoms, or $-O^-M^+$ where M^+ is a cation forming a pharmaceutically acceptable salt; and

R_8, R_9, and R_{10} are independently hydrogen, fluorine, chlorine, bromine, trifluoromethyl or nitro.

Other preferred compounds of the invention are those where Ar is a substituted benzothiazole, i.e., compounds of Formula III:



III

wherein

A is a C_1-C_4 alkylene group optionally substituted with C_1-C_2 alkyl;

Z is a bond, or C_1-C_3 alkylene optionally substituted with C_1-C_2 alkyl;

R_a is hydrogen, C_1-C_6 alkyl, chloro, bromo, fluoro, or trifluoromethyl;

R_1 is hydrogen, C_1-C_6 alkyl, halogen, preferably chloro or fluoro, or phenyl optionally substituted with with up to three groups independently selected from halogen, C_1-C_6

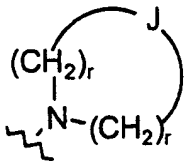
alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2, R_3, R_4 and R_5 are each independently hydrogen, halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR_7, SR_7, $S(O)R_7$, $S(O)_2N(R_7)_2$ $C(O)N(R_7)_2$ or $N(R_7)_2$, wherein each R_7 is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

a group of the formula



where

J is a bond, CH_2, oxygen, or nitrogen; and

each r is independently 2 or 3;

R_6 is hydroxy, C_1-C_6 alkoxy, or $-O^-M^+$ where M^+ is a cation forming a pharmaceutically acceptable salt; and

R_{11}, R_{12}, R_{13} and R_{14} are independently hydrogen, halogen, nitro, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkylsulfinyl, or C_1-C_6 alkylsulfonyl.

In preferred compounds of Formula III, the R_2, R_3, R_4 and R_5 substituents, in combination, represent one of bromo, cyano or nitro, one or two of fluoro, chloro, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or trifluoromethyl, or two fluoro or two methyl with one hydroxy or one (C_1-C_6)alkoxy, or one or, preferably, two fluoro and one methyl, or three fluoro groups. Particularly preferred R_2, R_3, R_4 and R_5 substituents are, independently, fluorine, chlorine, nitro, and trifluoromethyl.

In preferred compounds of Formulas II and III, A is preferably methylene, methylene substituted with a methyl group, or ethylene.

Preferred compounds according to Formula II above include those wherein R_8 is fluorine, R_9 is hydrogen and R_{10} is bromine or those wherein R_8 and R_{10} are hydrogens and R_9 is nitro.

Preferred compounds of Formula III above are thosewherein the benzothiazole moiety is substituted with nitro, one, two, or three of fluoro, one or two of chloro, or at least one

trifluoromethyl group. More preferred compounds of Formula II are those where A is methylene, R_1 is hydrogen or methyl, Z is a bond, and R_6 is hydroxy or C_1-C_6 alkoxy.

Still more preferred compounds of Formula II are those wherein R_{11}, R_{12} and R_{14} are fluorines and R_{13} is hydrogen. Other more preferred compounds of Formula II are those where R_a is methyl or hydrogen, Z is methylene or, more preferably, a bond, A is CHF or C_1 or C_2 alkylene, preferably methylene, R_1 is methyl or hydrogen, and R_{11}, R_{12} and R_{14} are halogens or C_1-C_3 alkyl. Still other more preferred compounds of Formula III are those where R_a is methyl or hydrogen, Z is methylene or, more preferably, a bond, A is CHF or C_1 or C_2 alkylene, R_1 is methyl or hydrogen, and R_{11}, R_{12} and R_{14} are fluorines or chlorines.

Particularly preferred compounds of Formula I are those where R_3 and R_4 are independently hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or halogen, and R_a is methyl or hydrogen, Z is a bond, A is methylene, methyl substituted methylene, or ethylene, R_1 is methyl or hydrogen, and R_{11}, R_{12} and R_{14} are fluorines or chlorines.

The term "prodrug group" denotes a moiety that is converted in vivo into the active compound of formula I wherein R_6 is hydroxy. Such groups are generally known in the art and include ester forming groups, to form an ester prodrug, such as benzyloxy, di(C_1-C_6)alkylaminoethyloxy, acetoxymethyl,

pivaloyloxymethyl, phthalidoyl, ethoxycarbonyloxyethyl, 5-methyl-2-oxo-1,3-dioxol-4-yl methyl, and (C_1-C_6)alkoxy optionally substituted by N-morpholino and amide-forming groups such as di(C_1-C_6)alkylamino. Preferred prodrug groups include hydroxy, C_1-C_6 alkoxy, and O^-M^+ where M^+ represents a cation. Preferred cations include sodium, potassium, and ammonium. Other cations include magnesium and calcium. Further preferred prodrug grops include O^-M^{++} where M^{++} is a divalent cation such as magnesium or calcium.

In certain situations, compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

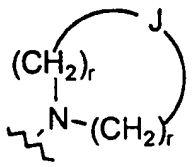
Representative compounds of the present invention include the pharmaceutically acceptable acid addition salts of compounds where R_6 includes basic nitrogen atom, i.e, an alkylamino or morpholino group. In addition, if the compound or prodrug of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of

the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH_2)n-ACOOH where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

As used herein, the terms 2-benzothiazolyl and benzothiazol-2-yl are synonymous.

Representative groups of the formula



include those where J is oxygen and each r is 2 (morpholinyl), J is nitrogen and each r is 2 (piperazinyl) or one r is 2 and the other 3 (homopiperazinyl), or J is CH_2 and each r is 2 (piperidinyl) or one r is 2 and the other 3 (homopiperidinyl).

Preferred groups of this formula are morpholinyl and piperazinyl.

The heterocyclic 5-membered ring having one to three nitrogen atoms, one of which may be replaced by oxygen or sulfur includes imidazolyl, oxazolyl, thiazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, and triazolyl.

The heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur includes triazinyl, pyrimidyl, pyridazinyl, oxazinyl and triazinyl.

The heterocyclic ring may be condensed with benzo so that said ring is attached at two neighboring carbon atoms to form a phenyl group. Such benzoheterocyclic ring may be attached to Z either through the heterocyclic group or through the benzo group of the benzoheterocyclic ring. Specific wherein said heterocyclic ring is condensed with a benzo include benzoxazolyl, quinazolin-2-yl, 2-benzimidazolyl, quinazolin-4-yl and benzothiazolyl. The oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms include positional isomers such as oxazolo[4,5-b]pyridine-2-yl, thiazolo[4,5-b]pyridine-2-yl, oxazolo[4,5-c]pyridine-2-yl, thiazolo[4,5-c]pyridine-2-yl, oxazolo[5,4-b]pyridine-2-yl, thiazolo[5,4-b]pyridine-2-yl, oxazolo[5,4-c]pyridine-2-yl, and thiazolo[5,4-c]pyridine-2-yl.

The following compounds of the invention are provided to give the reader an understanding of the compounds encompassed by the invention:

3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

5-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

2-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

7-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

3-methyl(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-2 propionic acid

3-methyl(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-3 propionic acid

3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid

5-methyl-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid

3-(3-nitrophenyl)methyl-indole-*N*-acetic Acid

The above compounds, further described in the Examples and other description of the invention below, are illustrative but are not meant to limit in any way the scope of the contemplated compounds according to the present invention.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or

adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such

as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives,

for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums,

for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or

diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

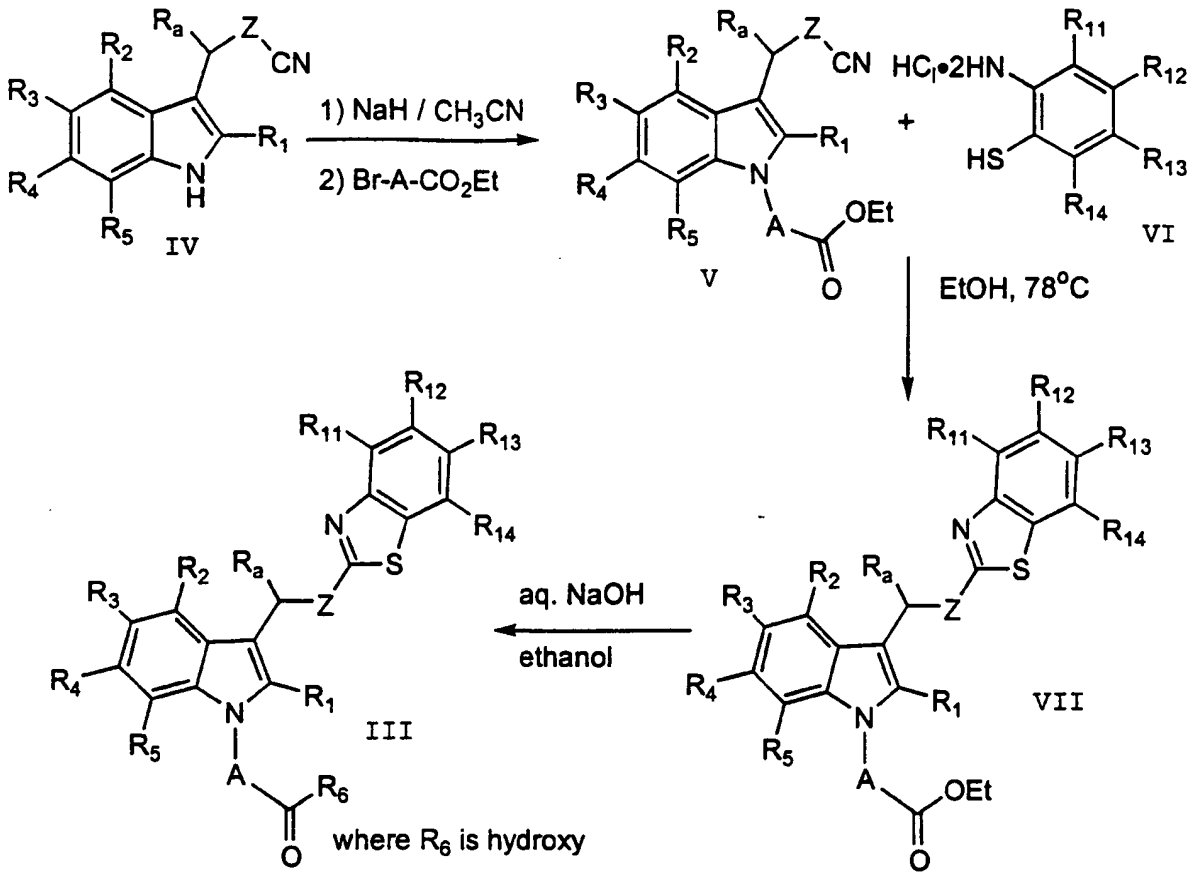
Dosage levels on the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 1000 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be prepared by use of known chemical reactions and procedures. General methods for synthesizing the compounds are presented below. It is understood that the nature of the substituents required for the desired target compound often determines the preferred method of synthesis. All variable groups of these methods are as described in the generic description if they are not specifically defined below. More detailed procedures for particular examples are presented below in the experimental section.

Methods of Preparation

The compounds of the invention where Ar is benzothiazolyl can be conveniently prepared from a substituted indole moiety using general Scheme A set forth below.



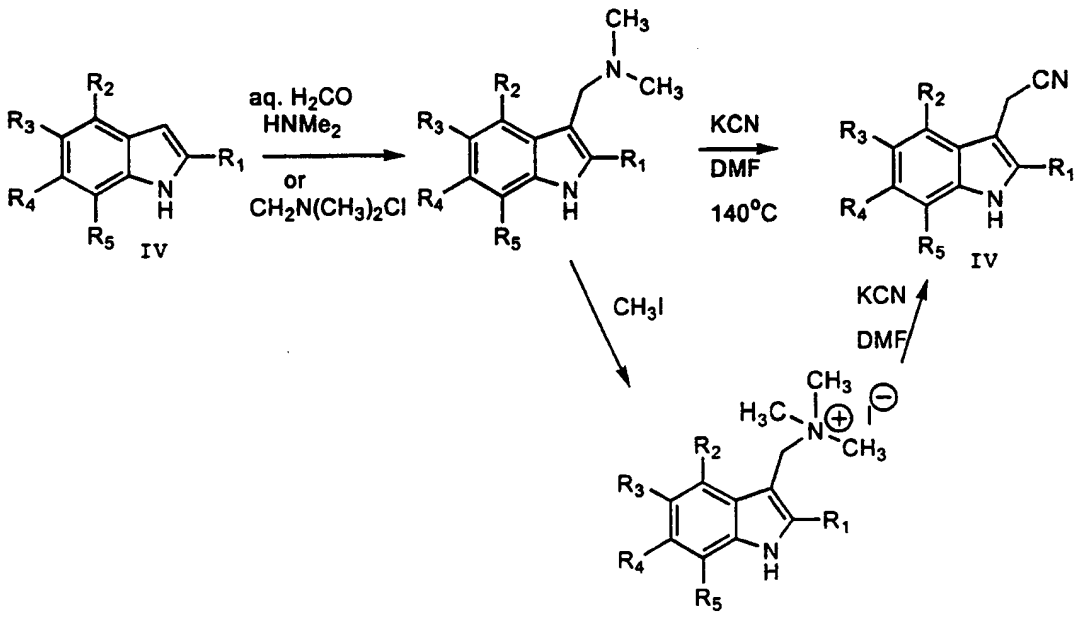
Scheme A

Treatment of a nitrile indole IV with a strong base such as, for example, sodium hydride, butyl lithium or sodium tert-butoxide, in a polar aprotic solvent such as acetonitrile, tetrahydrofuran or *N,N*-dimethylformamide followed by an treatment with an alkylating agent, e.g., ethyl or *tert*-butyl bromoacetate, provides the desired *N*-alkylated product V. Alternativly, phase transfer catalysis can be used in a biphasic solvent system. A general review of such alkylations can be found in Sundberg, R. J. *Indoles*; Chapter 11, Academic Press Inc., San Diego, CA, 1996. Condensation with a suitable 2-amino thiophenol hydrochloride salt VI provides

benzothiazole intermediate VII. These reactions are most often carried out in an alcohol solvents at elevated temperatures; however, other solvents like *N,N*-dimethylformamide and *N*-methylpyrrolidone can be used or the reactions can be carried out in the absence of solvents altogether. The scope of the reaction conditions useful for this transformation have been described previously (U.S. Pat. No. 5,700,819). General methods for the preparation of various substituted 2-amino thiophenols are also well known (*J. Med. Chem.* **1991**, *34*, 108 and *Chem. Pharm. Bull.* **1994**, *42*, 1264). In general, the best method of synthesis is determined by such factors as availability of starting materials and ease of synthesis. Deprotection of the alkanoic acid moiety VII can be carried out by methods common to those skilled in the art to result in compounds of Formula III. The method used in the deprotection depends on the type of protecting group. A description of such protecting groups and methods for deprotecting them may be found in: *Protective Groups in Organic Synthesis*, Second Edition, T. W. Green and P. G. M. Wuts, John Wiley and Sons, Ney York, **1991**. When a methyl or ethyl ester is used, an aqueous sodium hydroxide solution in ethanol or dimethoxyethane is conveniently employed for its removal.

If not commercially available, nitrile IV can be prepared substantially as described below in Scheme B depicting the formation of 3-acetonitrile substituted indoles of Formula IV

where Z is a bond. Thus, an indole moiety in a weak acid solution, for example, acetic acid in ethanol, is treated with aqueous formaldehyde and dimethyl amine in an alcohol solvent. The 3-(dimethylamino)methyl indole product can then be treated with sodium or potassium cyanide in *N,N*-dimethylformamide at elevated temperatures to provide the 3-acetonitrile substituted indole intermediate. Alternatively, an iminium salt like *N,N*-dimethylmethyleneammonium chloride can be used to prepare the 3-(dimethylamino)methyl indole intermediate.



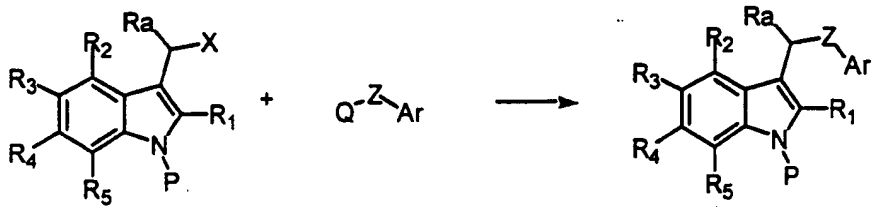
Scheme B

The 3-(dimethylamino)methyl indole intermediate can also be converted to the the 3-acetonitrile substituted indole intermediate via the trimethyl ammonium salt. The salt can be prepared by treating the gramine intermediate with an

alkalating agent like methyl iodide. The trimethyl ammonium salt intermediate can then be converted to the nitrile by treatment with sodium or potassium cyanide in a solvent like *N,N*-dimethylformamide. In general, the conversion to the acetonitrile occurs under more mild conditions when the trimethyl ammonium salt is used.

Alternatively, other compounds, such as those where Z-Ar represents a wide variety of substituted hetercycles, may be prepared using the general method outlined in Scheme C. Here, substituted indole intermediates where X is an activating group like hydroxyl, halogen, dialkyl amino, trialkyl ammonium or benzotriazole are coupled with Q-Z-Ar groups using methods well-established in indole chemistry. Examples of these methods where Q is Na or H and Z is sulfur, oxygen, nitrogen carbon or a bond are described in (A) Tidwell, J.H.; Peat, A.J.; Buchwald, S.L. *J. Org. Chem.* **1994**, *59*, 7164; (B) Bruneau, P.; Delvare, C.; Edwards, M.P.; McMillan, R.M. *J. Med. Chem.* **1991**, *34*, 1028; (C) Gan, T.; Cook, J.M. *Tetrahedron Lett.* **1997**, *38*, 1301; (D) Cerreto,F.; Villa, A.; Retico, A.; Scalzo, M. *Eur. J. Med. Chem.* 1992, 27 701; (E) Majchrzak, M.W.; Zobel, J.N.; Obradovich, D.J.; *Synth. Commun.* **1997**, *27*, 3201; (F) DeLeon, C.Y.; Ganem, B. *J. Org. Chem.* **1996**, *61*, 8730; (G) Katritzky, A.R.; Toader, D; Xie, L. *J. Org. Chem.* **1996**, *61*, 7571.

It is understood that, depending on the specific chemistry used, a protecting group, P, may be required. In general, P represents groups such as acyloxy, alkyl, sulfonyl or A-COOR. The use of these general methods is illustrated in *Protective Groups in Organic Synthesis*, Second Edition, T. W. Green and P. G. M. Wuts, John Wiley and Sons, Ney York, **1991**.

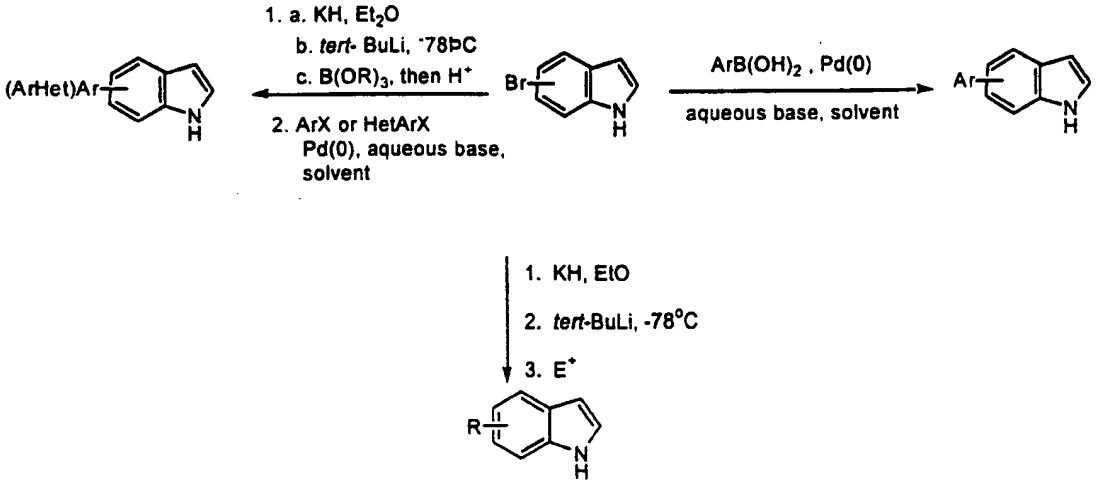


Scheme C

In general, the intermediate compounds wherein R_{2-6} is aryl or heteroaryl can be synthesized by the chemistry illustrated in reaction Scheme D below. For example, treatment of the potassium salt of an optionally substituted bromoindole with tert-butyllithium at low temperature in an ethereal solvent such as ether or tetrahydrofuran followed by the addition of an electrophile represents a general method for obtaining substituted indoles, as described by Rapoport, H. (*J. Org. Chem.* **1986**, *51*, 5106). For a discussion of a synthesis where R is acyl, see *Biorg. Med. Chem. Lett.* **1999**, 9, 333; where R is, thiomethyl, see *Heterocycles*, 1992, *34*, 1169; and where R is cycloalkyl, *see J. Med. Chem.* 1999, 42, 526.

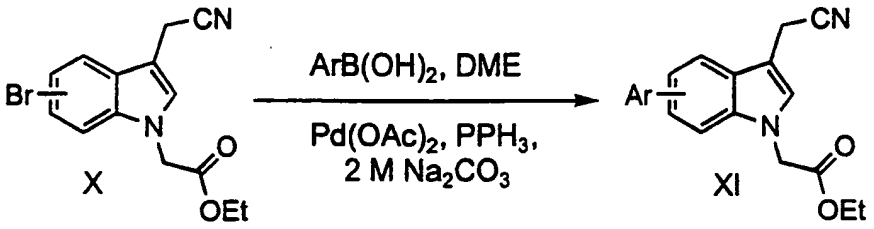
More specifically the addition of a trialkyl borate followed by an acidic work-up provides the desired indole boronic acids (*Heterocycles*, **1992**, *34*, 1169). Indole boronic acids can be used in well established transition metal catalyzed coupling reactions like the Suzuki reaction to provide aryl and heteroaryl indoles. These reactions are most often carried out in a mixture of ethereal or alcohol solvents with aqueous base in the presence of palladium catalyst, such as $Pd(OAc)_2$, $Pd(OAc)_2$ w/ PPh_3 or $Pd(PPh_3)_4$ as described in *Tetrahedron Lett.* **1998**, *39*, 4467, *J. Org. Chem.* **1999**, *64*, 1372 and *Heterocycles* **1992**, *34*, 1395.

Alternatively, an optionally substituted bromoindole can be treated with an arylboronic acid and a palladium catalyst to provide arylindoles in large quantities (*Synlett* **1994**, 93). A general review of Suzuki cross-couplings between boronic acids and aryl halides can be found in Miyaura, N; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.



Scheme D

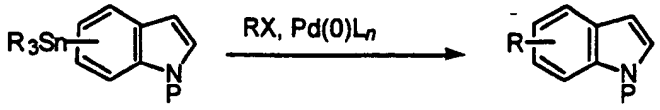
For example, treatment of the advanced intermediate indole X with an aryl or heteroaryl boronic acid using Pd-mediated coupling conditions provides the desired aryl and heteroaryl indole product XI as shown in scheme (E). In general the utility of this method is determined by the ease of synthesis of advanced intermediates of type X and the commercial availability of aryl and heteroaryl boronic acids.



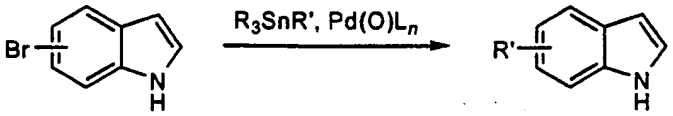
Scheme E

In addition, certain organometallic reactions eliminate the need for de novo construction of the indole nucleus. For example, the Stille reaction serves as a general method for the synthesis of regiocontrolled substitution of indole intermediates as described by Farina, V.; Krishnamurthy, V; Scott, W., *Organic Reactions*, **1998**, *50*, 1-652. As indicated in the scheme below, the indole may serve as the organotin species or the aryl halide. The stannylindole (XII), where P is a suitable protecting group such as [2-(trimethyl)ethoxy]methyl (SEM) or an alkyl substituent, is treated with a variety of partners (i.e., vinyl/allylic halides, vinyl triflates, aryl/heteroaryl halides and acyl halides) in the presence of a

$Pd(0)L_n$ catalyst to provide the desired indoles (XII) (*Synnlett* **1993**, 771, *Helv. Chim. Acta* **1993**, *76*, 2356 *and J. Org. Chem.* **1994**, *59*, 4250). Conversely, a haloindole (XIV) is treated with a variety of tin reagents under Stille conditions to provide the desired substituted indoles (XV) as described in *Heterocycles* **1988**, *27*, 1585 and *Synth. Comm* **1992**, *22*, 1627).

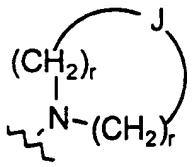


XII XIII



XIV XV

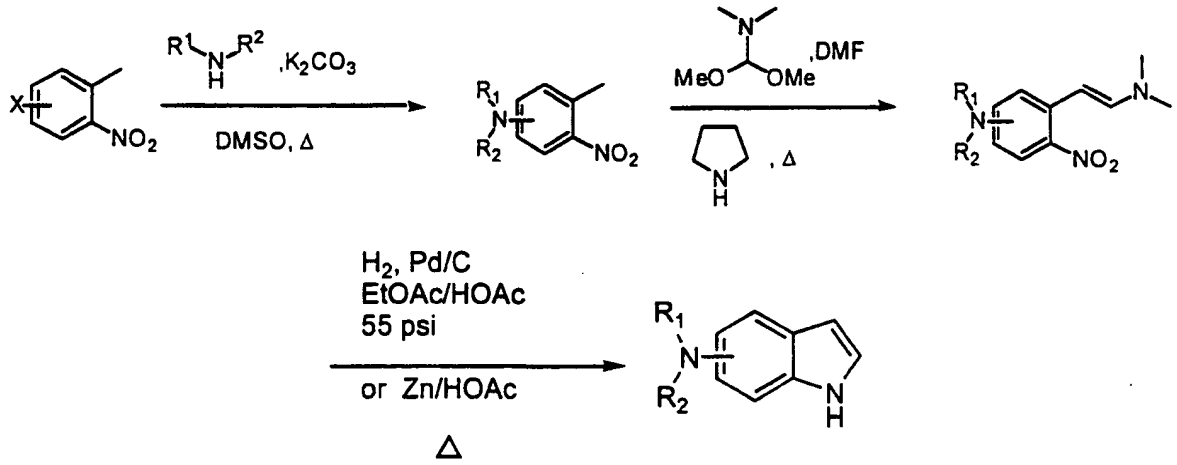
A general procedure for the synthesis of intermediate compounds using amines of the formula NR_xR_{x2} (NR_1R_2 in the scheme below) is given in scheme F below. In Scheme F, R_x and R_{x2} are the same or different and represent hydrogen, C_1-C_6 alkyl, or R_x and R_{x2} together represent a group of the formula:



where J and each r is as defined above for formula I.

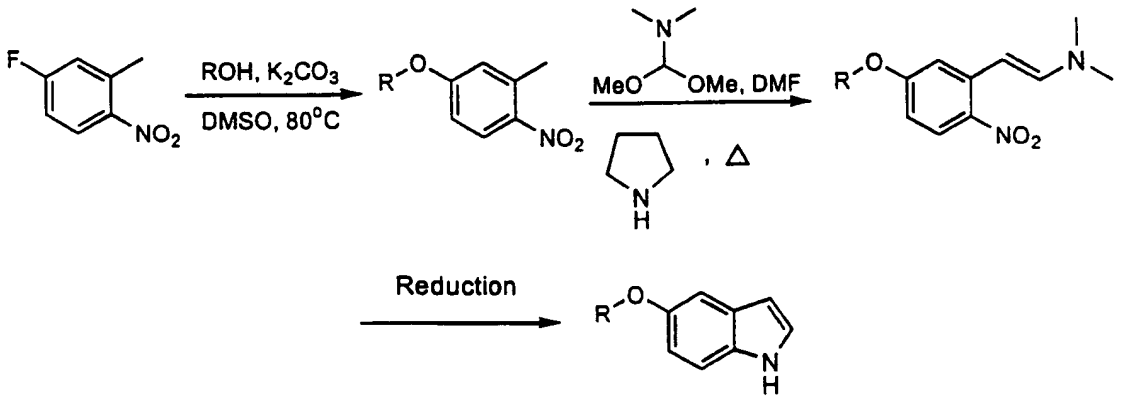
As shown in Scheme F, nucleophilic substitution of X (X is halogen, preferably fluorine) in an aromatic system is a method

often used to substitute aromatic rings with amine and ether functionalities. Both 4- and 5- fluoro-2-nitrotoluene are sufficiently activated to undergo substitution with amines in the presence of K_2CO_3 in a polar aprotic solvent such as, for example, DMSO as described in *J. Med. Chem.* **1993**, *36*, 2716. The Leimgruber -Batcho two-step method is a general process for the construction of the indole ring system from the appropriate *o*-nitrotoluene. This reaction involves the condensation of an *o*-nitrotoluene with *N,N*-dimethylformamide dimethyl acetal followed by a reductive cyclization under suitable conditions such as hydrogen over a palladium catalyst or Zn/HOAc as described in Sundberg, R.J. *Indoles;* Chapter 2, Academic Press Inc., San Diego, CA, 1996. A representative description of the process can also be found in *Organic Synthesis*, **1984**, *63*, 214.



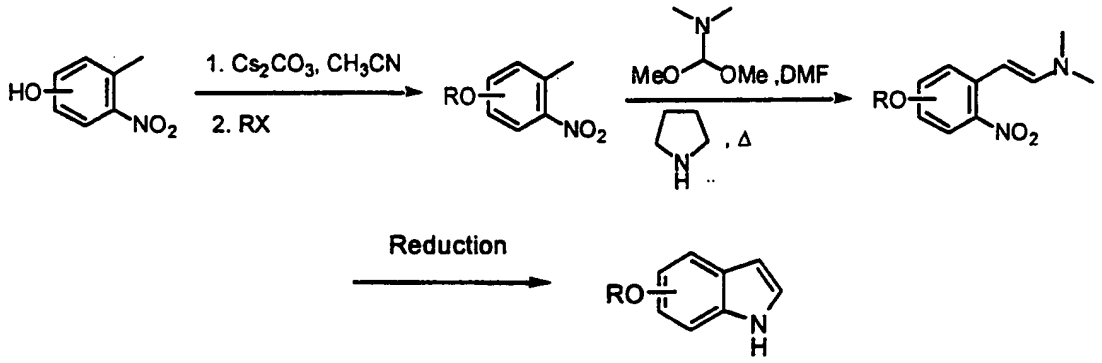
Scheme F

A general procedure for the synthesis of intermediate compounds wherein R is an aromatic, heteroaromatic or alkyl group is indicated in Scheme G below. As previously described, nucleophilic substitution of halogen, preferably fluorine, in an aromatic system is a method often used to substitute aromatic rings with amine and ether functionalities. Both 4- and 5-fluoro-2-nitrotoluene are sufficiently activated enough to undergo substitution with alcohols or phenols in the presence of K_2CO_3 in a polar aprotic solvent such as DMSO. A similar system using KOH and phenol is described in *J. Med. Chem.* **1994**, *37*, 1955. Alternatively, solid-liquid phase transfer catalysis (PTC) methods have been used to prepare intermediate ethers of this type as described in *Synth. Comm.* **1990**, *20*, 2855. The appropriately substituted *o*-nitrotoluene can then be converted to the appropriate indole by the Leimgruber-Batcho method previously desribed.



Scheme G

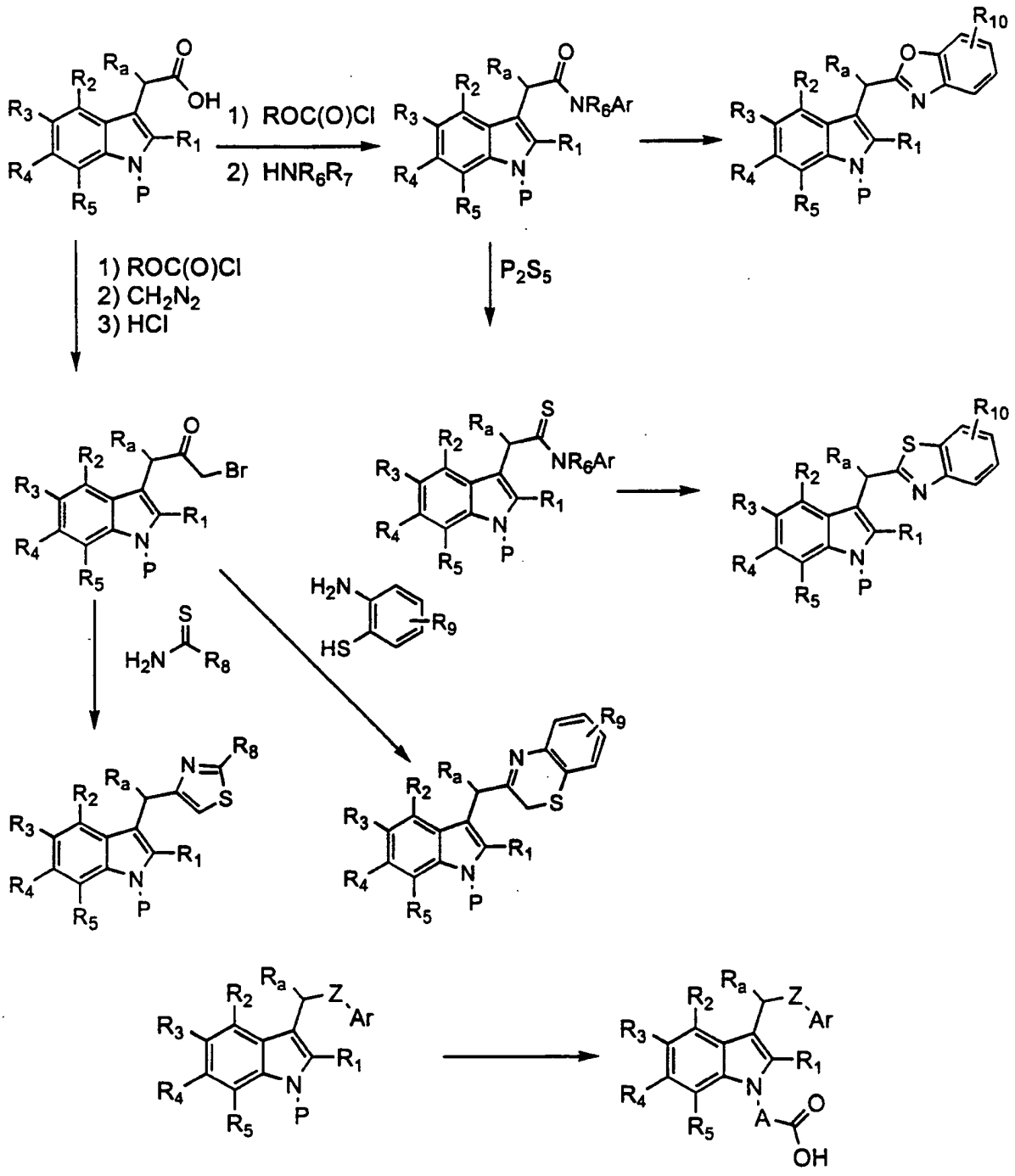
The preparation of intermediate alkoxy indole compounds wherein R is C_1-C_6 alkyl is outlined in Scheme H below. Commercially available nitrophenols can be alkylated under mild conditions with a base such as, for example, K_2CO_3 or Cs_2CO_3, in a polar aprotic solvent, e.g. CH_3CN, with a variety of suitable alkyl halides. See *Synth. Comm.* **1995**, *25*, 1367. The alkoxy *o*-nitrotoluene can then be converted to the desired indole as described above.



Scheme H

Alternatively, some examples of the invention where Z is a bond and Ar is a substituted heterocycle such as a thiazole; or Z is amide and Ar is a substituted phenyl can be conveniently prepared from an indole 3-acetic acid derivative as illustrated in Scheme I. Using this method, the carboxylic acid moiety is activated and coupled with an aryl amine. Some examples of activating methods well-known to those skilled in the art include formation of acid chloride, mixed anhydrides and coupling reagents such as 1,3-dicyclohexylcarbodiinide (DCC).

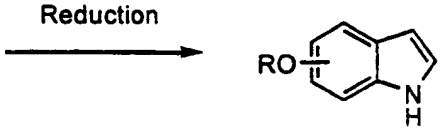
A review of such method can be found in Bodanszky, M. *Principles of Peptide Synthesis*; Springer-Verlag: New York, 1984. For the examples where Z is a bond and Ar is a substituted benzothiazole or benzoxazole, the intermediate amide or thioamide can be cyclized into the aromatic ring. Examples of these types of hetercycle forming reactions are described in Mylar, B. L. et al. *J. Med. Chem.* **1991**, 34, 108. In addition, the carboxylic acid can be converted to a chloro- or bromomethyl ketone and condensed with nucleophiles like thioamides or 2-aminothiophenols to produce thiazole or benzothiazine derivatives. Examples of methods to prepare the chloro- and bromomethyl ketones are illustrated in Rotella, D.P.; *Tetrahedron Lett.* **1995**, *36*, 5453 and Albeck, A.; Persky, R.; *Tetrahedron* **1994**, *50*, 6333. Depending on the reaction conditions in a given synthetic sequence a protecting group may be required. It is also understood that the specific order of steps used in the synthesis depends on the particular example being prepared. P may represent H, A-COOH, A-COO-lower alkyl or a simple protecting group that can be removed at a late stage of the synthesis. When such a protecting group is used, the A-CO2R6 group can be introduced near the end of the synthesis after the Z-Ar group has been assembled. Method of introducing the Z-Ar group are similar to those already described.



Scheme I

Another strategy involves the synthesis of substituted indoles via an intramolecular cyclization of an aniline

nitrogen onto a substituted alkyne as shown in Scheme J. Typical approaches utilize commercially available o-iodoaniline derivatives. When these intermediates are unavailable, the regioselective ortho iodination of aromatic amines is used to generate the required intermediate (*J. Org. Chem.* **1996**, 61, 5804). For example, Iodophenyl intermediates are treated with trimethylsilylacetylene in the presence of a Pd catalyst and a Cu(I) source, such as cupric iodide, to produce o-alkynylanilines. See *Heterocycles*, **1996**, 43, 2471 and *J. Org. Chem.* 1997, 62, 6507. Further elaboration of the o-alkynylaniline to the desired indole can be done by a copper-mediated cyclization or a base-induced amine ring closure onto the alkyne functionality (*J. Med. Chem.* **1996**, 39, 892). Alternative modifications have been made in the acetylenic derivatives to generate more elaborate indole structures as described *in J. Am. Chem. Soc.* **1991**, 113, 6689, *Tetrahedron Lett.* **1993**, 24, 2823 and *Tetrahedron Lett.* **1993**, 34, 6471.



Scheme J

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases,

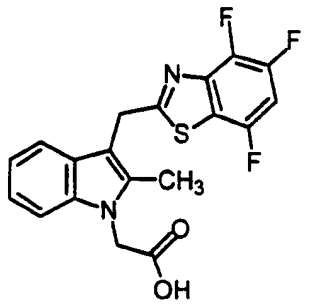
protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The preparation of the compounds of the present invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them.

Example 1:

Preparation of 2-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

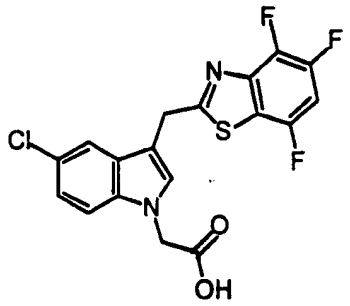


2-Methyl-3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 2-methylindole was used instead of 5-chloroindole in step 1: 178-180°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.75-7.62 (m, 1 H), 7.45 (d, *J* = 9.0 Hz, 1 H), 7.39 (d,

J = 9.0 Hz, 1 H), 7.08 (t, J = 9 Hz, 1 H), 6.99 (t, J = 9.0 Hz, 1 H), 5.00 (s, 2 H), 4.60 (s, 2 H), 2.38 (s, 3 H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; found 391.0 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_2S$: C, 58.46; H, 3.36; N, 7.18; S, 8.21. Found: C, 58.47; H, 3.29, N, 7.12, S, 8.18.

Example 2:

Preparation of 5-chloro-3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid



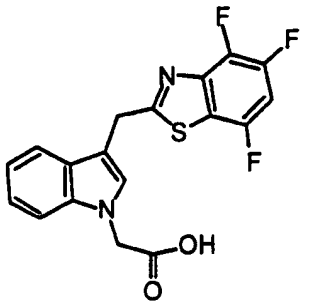
5-chloroindole-3-acetonitrile :

A solution of aqueous formaldehyde (37%, 2.95 mL, 66.0 mmol) and dimethylamine (40%, 5.30 mL, 66.0 mmol) in 20 mL EtOH was cooled to 0°C. 5-Chloroindole (4.0 g, 26.4 mmol) was dissolved in a HOAc:EtOH mixture (1:1, 40 mL) and added dropwise to the reaction mixture. After stirring at this temperature for 2 h, the mixture was allowed to warm to room temperature and stir overnight. The mixture was added to a sat'd solution of $NaHCO_3$. 1 N NaOH was added until the pH was between 9-10. The resulting mixture was extracted with CH_2Cl_2 (3X). The organics were combined and washed with a sat'd aq. NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo* to

(M + 1)$^+$. Anal. Calcd for $C_{18}H_{10}F_3N_2O_2SCl$: C, 52.63; H, 2.45; N, 6.82; S, 7.81. Found: C, 52.56; H, 2.40, N, 6.71, S, 7.72.

Example 3:

Preparation of 3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid



2,3,5,6-Tetrafluoroacetanilide:

A solution of 2,3,5,6-tetrofluoroaniline (200 g, 1.21 mol) in anhydrous pyridine (103 mL, 1.27 mol) was treated with acetic anhydride (120 mL, 1.27 mol) and heated to 120 °C for 2 h. After cooling to room temperature, the solution was poured into ice-cold water (500 mL). The resulting precipitate was filtered, dissolved in ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The solid material was washed with heptane (200 mL) and dried to give 2,3,5,6-tetrafluoroacetanilide as a white crystalline solid (206 g, 82%): mp 136-137 °C; R_f 0.48 (50% ethyl acetate in heptane); ^1H NMR (DMSO-d_6, 300 MHz) δ 10.10 (s, 1 H), 7.87-7.74 (m, 1 H), 2.09 (s, 3 H). Anal. Calcd for $C_8H_5F_4NO$: C, 46.39; H, 2.43; N, 6.67. Found C, 46.35; H, 2.39; N, 6.68.

2,3,5,6-Tetrafluorothioacetanilide:

A flame-dried, 4-necked 5,000 mL round-bottomed flask was charged with phosphorous pentasulfide (198 g, 0.45 mol) and diluted with anhydrous benzene (3,000 mL, 0.34 M). 2,3,5,6-tetrafluoroacetanilide (185 g, 0.89 mol) was added in one portion and the bright yellow suspension was heated to a gentle reflux for 3 h. The solution was cooled to 0 °C and filtered. The insoluble material was washed with ether (2 x 250 mL) and the combined filtrate was extracted with 10% aq. NaOH (750 mL, 500 mL). After cooling the aqueous layer to 0 °C, it was carefully acidified with conc. HCl (pH 2-3). The precipitated product was collected by filtration and washed with water (500 mL). The yellow-orange material was disolved in ethyl acetate (1,000 mL), dried over $MgSO_4$ and activated charcoal (3 g), filtered through a short pad of silica (50 g), and concentrated. The resulting solid was triturated with heptane (500 mL) and filtered to give 2,3,5,6-tetrafluorothioacetanilide (174.9 g, 88%): mp: 103-104°C; R_f 0.67 (50% ethyl acetate in heptane); ^1H NMR (DMSO-d_6, 300 MHz) δ 11.20 (s, 1 H), 8.00-7.88 (m, 1 H), 2.66 (s, 3 H). Anal. Calcd for $C_8H_5F_4NS$: C, 43.05; H, 2.26; N, 6.28. Found C, 43.10; H, 2.23; N, 6.19.

4,5,7-Trifluoro-2-methylbenzothiazole:

heated to a gentle reflux (125 °C) for 3 h. The solution was cooled to 0 °C and acidified to pH 3-4 using conc. HCl (appox. 200 mL). The solution was extracted with ether (750 mL) and washed with water (200 mL). The organic layer was dried over Na_2SO_4, filtered and treated with 2,2-di-*tert*-butyl-4-methylphenol (0.135 g, 0.5 mol%). After concentrating to dryness, the crude product was dissolved in anhydrous methanol (200 mL) and treated with an HCl solution in 1,4-dioxane (37 mL, 4 N, 148 mmol). The resulting mixture was concentrated to dryness, triturated with isopropylether (100 mL) and filtered to give 2-amino-3,4,6-trifluorothiophenol hydrochloride (19.3 g, 73%) as a light brown solid that was used without further purification. mp. 121-124 C; R_f 0.43 (30% ethyl acetate in heptane); Anal. Calcd for $C_6H_5ClF_3NS$: C, 33.42; H, 2.34; N, 6.50; S, 14.87. Found C, 33.45; H, 2.27; N, 6.48; S, 14.96.

3-cyanomethyl-indole-*N*-acetic acid, Ethyl Ester:

Under an atmosphere of nitrogen, a solution of 3-indolyl acetonitrile (25.0 g, 160 mmol) in dry acetonitrile (530 mL, 0.3 M) was treated with sodium hydride (95%, 4.2 g, 168 mmol) and stirred for 30 min. Ethyl bromoacetate (21.3 mL, 192 mmol) was added in a dropwise manner over 10 min and the solution was stirred at room temperature for 16 h. After concentrating under reduced pressure, the resulting residue was dissolved in ethyl acetate and washed with sat'd. aq. NaCl. The organic

extracts were dried over $MgSO_4$, filtered and concentrated. The crude product was recrystalized from heptane and ethyl acetate to give the target compound as a white crystalline solid (19 g, 49%): mp 98-99 °C; R_f 0.29 (30% ethyl acetate in heptane); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.59 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1 H), 7.40 (dd, J_1 = 8.1 Hz, J_2 = 0.6 Hz, 1 H), 7.36 (s, 1 H), 7.18 (b t, J = 7.2 Hz, 1 H), 7.10 (b t, J = 7.2 Hz, 1 H), 5.12 (s, 2 H), 4.14 (q, J = 7.2 Hz, 2 H), 4.06, (s, 2 H), 1.20 (t, J = 7.2 Hz, 3 H);); LRMS calcd for $C_{14}H_{14}N_2O_2$: 242.3; found 243.0 $(M + 1)^+$. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.49; H, 5.82; N, 11.56. Found C, 69.39; H, 5.89; N, 11.59.

3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, Ethyl Ester: Under a nitrogen atmosphere, a solution of 3-acetonitrile-indole-*N*-acetic acid, ethyl ester (11.0 g, 45.4 mmol) in anhydrous ethanol (90 mL, 0.5 M) was treated with 2-amino-3,4,6-trifluorothiophenol hydrochloride (12.7 g, 59.0 mmol) and heated to a gentle reflux for 16 h. After cooling to room temperature, the solution was concentrated under reduced pressure, diluted with ethyl acetate and washed with 2N HCl and sat'd. aq. NaCl. The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by MPLC (10-50% ethyl acetate in heptane, 23 mL/min, 150 min) to give 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester (6.0 g, 36%) as a white crystalline

solid: mp 110-111 °C; R_f 0.41 (30% ethyl acetate in heptane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.74-7.66 (m, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.46 (s, 1 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 7.15 (br t, *J* = 6.9 Hz, 1 H), 7.04 (br t, *J* = 7.8 Hz, 1 H), 5.14, s, 2 H), 4.66 (s, 2 H), 4.14 (q, *J* = 7.2 Hz, 3 H); LRMS calcd for $C_{20}H_{15}F_3N_2O_2S$: 404.4; found 405.0 $(M + 1)^+$. Anal. Calcd for $C_{20}H_{15}F_3N_2O_2S$; C, 59.40; H,3.74; N, 6.93; S, 7.93. Found C, 59.52; H, 3.721 N, 6.92; S, 8.04.

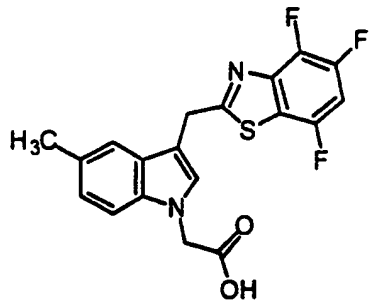
3-(4,5,7-trifluorobenzothiazol-2yl) methyl-indole-*N*-acetic acid:

A solution of give 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl ester (5.91 g, 14.6 mmol) in 1,2-dimethoxyethane (73 mL, 0.2 M) was cooled to 0 °C and treated with aq. NaOH (1.25 N, 58 mL, 73.1 mmol) in a dropwise manner over 15 min. After the addition was complete, the solution was stirred for an additional 30 min, acidified to pH 3 with 2N HCl, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with sat'd. aq. NaCl (30 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated. The resulting material was stirred as a supension in heptane, filtered and dried to give 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid (5.38 g, 98%) as a pale yellow solid: mp 177-178 °C; R_f 0.44 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ

7.74-7.65 (m, 1 H), 7.53 (d, J = 7.5 Hz, 1 H), 7.46 (s, 1 H), 7.40 (d, J = 8.1 Hz, 1 H), 7.15 (b t, J = 6.9 Hz, 1 H), 7.03 (b t, J = 7.2 Hz, 1 H), 5.03 (s, 2 H), 4.65 (s, 2 H); LRMS calcd for $C_{18}H_{11}F_3N_2O_2S$: 376.4; found 375.0 $(M - 1)^-$. Anal. Calcd for $C_{18}H_{11}F_3N_2O_2S$: C, 57.44; H, 2.95; N, 7.44; S, 8.52. Found C, 57.58; H, 2.99; N, 7.38; S, 8.51.

Example 4:

Preparation of 5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid



5-Methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 5-methylindole was used instead of 5-chloroindole in step 1: mp 131-133 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73-7.62 (m, 1 H), 7.39 (s, 1 H), 7.30 (s, 1 H), 7.27 (d, J = 9.0 Hz, 1 H), 6.96 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H), 4.98 (s, 2 H), 4.60 (s, 2 H), 2.32 (s, 3 H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; found 391.0 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_2S$: C, 58.46; H, 3.36; N, 7.18; S, 8.21. Found: C, 58.36; H, 3.30, N, 7.10, S, 8.20.

Example 5:

Preparation of 7-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

7-Methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 7-methylindole was used instead of 5-chloroindole in step 1: mp 216-218 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73-7.63 (m, 1H), 7.36-7.32 (m, 2 H), 6.92-6.88 (m, 2 H), 5.17 (s, 2 H), 4.60 (s, 2 H), 2.55 (s, 3 H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; found 391.0 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_2S$: C, 58.46; H, 3.36; N, 7.18; S, 8.21. Found: C, 58.37; H, 3.37; N, 7.11; S, 8.13.

Example 6:

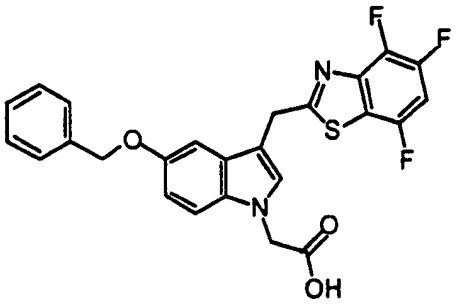
Preparation of 6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

6-Chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 6-chlorolindole was used instead of 5-chloroindole in step 1: mp 194-195°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73-7.63 (m, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.46-7.42 (m, 2 H), 7.00 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1 H), 4.76 (s, 2 H), 4.62 (s, 2 H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 410.0; found 411.0 $(M + 1)^+$. Analysis calculated for $C_{18}H_{10}F_3N_2O_2SCl$: C,

52.63; H, 2.45; N, 6.82; S, 7.81. Found: C, 52.50; H, 2.44, N, 6.74, S, 7.69.

Example 7:

Preparation of 5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid



5-Benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 5-benzyloxyindole was used instead of 5-chloroindole in step 1: mp 165-168°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73-7.65 (m,1 H) 7.40-7.30 (m, 3 H), 7.28-7.10 (m, 4 H), 7.10 (d, J = 2.4 Hz, 1 H), 6.87-6.80 (m, 1 H), 5.05 (s, 2 H), 4.95 (s, 2 H), 4.57 (s 2 H); LRMS calcd for $C_{25}H_{17}F_3N_2O_2S$: 482.0; found 483.0 $(M + 1)^+$.

Example 8:

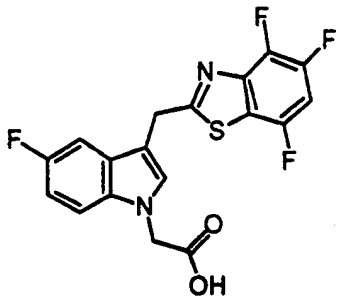
Preparation of 6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 6-fluoroindole was used instead

of 5-chloroindole in step 1: mp 200-203 C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73-7.65 (m, 1 H), 7.53 (dd, J_1 = 8.4 Hz, J_2 = 3.3 Hz, 1 H), 7.44 (s, 1 H), 7.34 (dd, J_1 = 10.5 Hz, J_2 = 2.4 Hz, 1 H), 6.93-6.68 (m, 1 H), 5.11 (s, 2 H), 4.64 (s, 2 H); LRMS calcd for $C_{18}H_{10}F_4N_2O_2S$: 394.0; found 395 (M + 1).

Example 9:

Preparation of 5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid



5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 5-fluoroindole was used instead of 5-chloroindole in step 1: mp 193-195°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.65 (m, 1 H), 7.51 (s, 1 H), 7.42 (br dd, J_1 = 9.0 Hz, J_2 = 4.8 Hz, 1 H), 7.34 (br dd, J_1 = 9.9 Hz, J_2 = 2.4 Hz, 1 H), 7.02-6.96 (m, 1 H), 5.03 (s, 2 H), 4.62 (s, 2 H); LRMS calcd for $C_{18}H_{10}F_4N_2O_2S$: 394.0; found 395 (M + 1).

Example 10:

Preparation of 6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid

6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 2, except 6-methylindole was used instead of 5-chloroindole in step 1: mp 211-213°C, R_f0.50 (10% methanol in diehloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) 7.72-7.63 m, 1 H), 7.37 (d, *J* = 7.1 Hz, 1 H), 7.35 (s, 1 H), 7.18 (s, 1 H), 6.85 (d, *J*=8.4 Hz, 1 H), 5.08 (s, 2 H), 4.60 (s, 2 H), 2.37 (s, 3 H).

Example 11:

Preparation of 3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic Acid

3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic Acid was prepared in a manner analogous to that set forth in Example 3 (steps 5-7), except 2-amino-4-(trifluoromethyl)-benzenethiol hydrochloride was used instead of 2-amino-3,4,6-trifluorothiophenol hydrochloride in step 6: mp 233-234 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.29 (s, 1 H), 8.19 (br d, *J* = 8.1 Hz, 1 H), 7.68 (br d, *J* = 9.0 Hz, 1 H), 7.49 (br d, *J* = 6.9 Hz, 1 H), 7.41 (s, 1 H), 7.38 (br d, *J* = 8.4 Hz, 1 H), 7.12 (br t, *J* = 6.9 Hz, 1 H), 7.00 (br t, *J* = 6.9 Hz, 1 H), 5.01 (s, 2 H), 4.60 (s, 2 H).

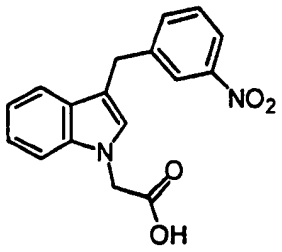
Example 12:

Preparation of 5-Methyl-3-(5-Trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid

5-Methyl-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid was prepared in a manner analogous to that set forth in Example 2, except 5-methylindole was used instead of 5-chloroindole in step 1 and, 2-amino-4-(trifluoromethyl)-benzenethiol hydrochloride was used instead of 2-amino-3,4,6-trifluorothiophenol hydrochloride in step 2 (Example 3, step 6): mp 248-249°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.27 (s, 1 H), 8.20 (d, J = 8.4 Hz, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.35 (s, 1 H), 7.27 (s, 1 H), 7.25 (d, J = 8.1 Hz, 1 H), 6.95 (d, J = 8.1 Hz, 1 H), 4.96 (s, 2 H), 4.57 (s, 2 H), 2.31, (s, 3 H); LRMS calcd for $C_{20}H_{15}F_3N_2O_2S$:; found 405 (M + H).

Example 13:

Preparation of 3-(3-nitrophenyl)methyl-indole-*N*-acetic acid



Preparation of indole-N-acetic acid, ethyl ester

Under an atmosphere of nitrogen, a solution of indole (15.0 g, 128 mmol) in dry acetonitrile (300 mL, 0.4 M) was

treated with sodium hydride (95%, 3.69 g, 153 mmol) and stirred for 30 min. Ethyl bromoacetate (17.0 mL, 153 mmol) was added in a dropwise manner over 10 min and the solution was stirred at room temperature for 16 h. After concentrating under reduced pressure, the resulting residue was dissolved in ethyl acetate and washed with sat'd. aq. NaCl. The organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (50% ethyl acetate in heptane): Rf0.25 (40% ethyl acetate in heptane) ^1H NMR (DMSO-d_6, 300 MHz) δ 7.53 (d, J = 6.3 Hz, 1 H), 7.38-7.31 (m, 2 H), 7.11 (br t, J = 7.2 Hz, 1 H), 7.02 (br t, J = 7.2 Hz, 1 H), 6.45-6.43 (m, 1 H), 5.10 (s, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 1.19 (t, J = 7.2 Hz, 3 H).

Preparation of 3-(3-nitrophenyl)methyl-indole-*N*-acetic acid, ethyl ester

Indole-*N*-acetic acid, ethyl ester (0.500 g, 2.50 mmol) was dissolved in 1,4-dioxane (5 mL) at room temperature with stirring. To this solution was added Ag_2CO_3/Celite (50% by weight, 0.500 g, 0.9 mmol). The mixture was warmed to 90°C and maintained overnight. H_2O was added to the reaction mixture followed by extracted with EtOAc (2X). The organics were combined and washed with a sat'd brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was

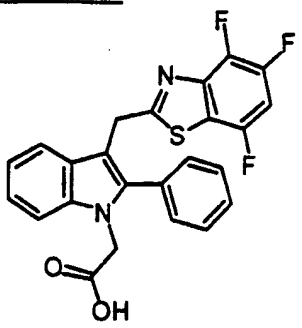
purified by SiO_2 flash chromatography (3:2 Heptane: EtOAc) to give 180 mg (22%) as a pale yellow oil. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.10 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1 H), 7.75 (d, *J* = 7.2 Hz, 1 H), 7.59-7.57 (m, 1 H), 7.46-7.39 (m, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.20 (s, 1 H), 7.13-6.89 (m, 2 H), 5.06 (s, 2 H), 4.19 (s, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 1.18 (t, *J* = 7.2 Hz, 3 H).

Preparation of 3-(3-nitrophenyl)methyl-indole-*N*-acetic Acid

3-(3-Nitrophenyl)methyl-indole-*N*-acetic Acid, ethyl ester (0.175 g, 0.5 mmol) was dissolved in THF: EtOH (1:4, 5 mL) at room temperature with stirring. The mixture was cooled to 0°C and treated with 1N NaOH (1.55 mL, 1.6 mmol). The mixture was allowed to stir at this temperature for 2 h. 1 N HCl was added and the mixture extracted with EtOAc (2X). The organics were combined and washed with a sat'd brine solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated with heptane and vacuum- filtered with several heptane washings to give 110 mg (69%) the desired compound as an off-white powder. mp 163-165 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.11 (s, 1 H), 8.03 (d, *J* = 8.1 Hz, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.53 (t, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.20 (s, 1 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 6.97 (t, *J* = 7.2 Hz, 1 H), 4.96 (s, 2 H), 4.18 (s, 2 H); LRMS calcd for $C_{17}H_{14}N_2O_4S$: 310.0; found 311 $(M + 1)^+$.

Example 14

Preparation of 2-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid



2-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 2-phenylindole was used instead of 5-chloroindole in step 1: mp 238-239°C; R_f 0.60 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.60-7.70 (m, 1H), 7.39-7.58 (m, 7H), 7.20 (t, *J* = 9 Hz, 1H), 7.07 (t, *J* = 9 Hz, 1H), 4.80 (s, 2H), 4.45 (s, 2H); LRMS calcd for $C_{24}H_{15}F_3N_2O_2S$: 452.0; found 453.0 (M + 1)$^+$. Anal. Calcd for $C_{24}H_{15}F_3N_2O_2S$: C, 63.71; H, 3.34; N, 6.19; S, 7.09. Found: C, 63.46; H, 3.32; N, 6.11; S, 6.96.

Example 15

Preparation of 5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

3-cyanomethyl-5-phenyl-indole-*N*-acetic acid, ethyl ester

5-Bromo-3-cyanomethyl-indole-N-acetic acid, ethyl ester (1.0 g, 3.1 mmol) and phenylboronic acid (0.418 g, 3.4 mmol) were dissolved in anhydrous DME at room temperature under a

nitrogen atmsophere and treated with $Pd(OAc)_2$ (2.1 mg, 0.0093 mmol) and PPh_3 (7.4 mg, 0.028 mmol). This mixture was heated to reflux and 2 M Na_2CO_3 (3.11 mL, 6.2 mmol) was added *via* syringe. After 12h, the mixture was cooled to room temperature and added to H_2O (50mL). The resultant mixture was extracted with EtOAc (2X, 100mL) and the organics were combined and washed with a sat'd aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography (heptane to 1:1 heptane/ EtOAc) to give the desired material as a white solid (445 mg, 45%); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.64-7.74 (m, 4H), 7.39-7.44 (m, 4H), 7.29-7.34 (m, 1H), 5.20 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.08 (s, 2H), 1.20 (t, J = 7.2 Hz, 3H).

5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-*N*-acetic acid

5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 5-phenylindole was used instead of 5-chloroindole in step 1: mp 156-159 °C; R_f 0.55 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.66-7.69 (m, 4H), 7.57-7.60 (m, 1H), 7.39-7.47 (m, 3H), 7.29-7.35 (m, 2H), 5.06 (s, 2H), 4.66 (s, 2H); LRMS calcd for $C_{24}H_{15}F_3N_2O_2S$: 452.0; found 453.0 (M + 1)$^+$. Anal. Calcd for $C_{24}H_{15}F_3N_2O_2S$: C, 63.71; H, 3.34; N, 6.19; S, 7.09. Found: C, 63.54; H, 3.32; N, 6.13; S, 7.01.

Example 16

Preparation of 6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

Step 1: 6-Phenylindole

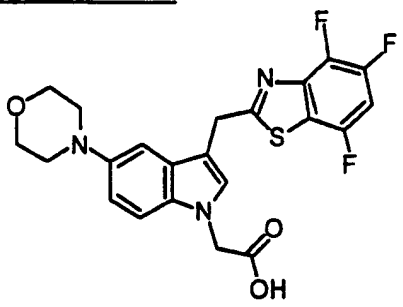
A solution of 6-bromoindole (2.0 g, 10.20 mmol) in anhydrous toluene (20mL) under a nitrogen atmosphere was treated with $Pd[P(Ph_3)]_4$ (10% mol). After stirring the mixture for 30 min., phenylboronic acid (1.87 g, 15.30 mmol) in anhydrous EtOH (10 mL) was added followed by the addition of sat'd $NaHCO_3$ (6mL). The bi-phasic mixture was heated to reflux for 24 h. After cooling to room temperature, the mixture was added to a sat'd brine solution and extracted with EtOAc (2X). The organic layer was dried over MgSO4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 CH_2Cl_2/ heptane) to give the desired material as white powder (900 mg, 45%): ^1H NMR (DMSO-d_6, 300 MHz) δ 11.15 (br s, 1H), 7.58-7.66 (m, 4H), 7.41-7.47 (m, 2H), 7.36 (m, 1H), 7.26-7.31 (m, 2H), 6.42 (m, 1H).

Preparation of 6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-*N*-acetic acid 6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 6-phenylindole was used instead of 5-chloroindole in step 1: mp 156-159°C; R_f 0.50 (10% methanol in chloroform);

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.65-7.75 (m, 4H), 7.57-7.62 (m, 1H), 7.41-7.50 (m, 3H), 7.26-7.38 (m, 2H), 5.12 (s, 2H), 4.68 (s, 2H); LRMS calcd for $C_{24}H_{15}F_3N_2O_2S$: 452.0; found 453.0 (M + 1)$^+$. Anal. Calcd for $C_{24}H_{15}F_3N_2O_2S$: C, 63.71; H, 3.34; N, 6.19; S, 7.09. Found: C, 63.46; H, 3.33; N, 6.10; S, 6.96.

Example 17

Preparation of 5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid



5-Morpholino-2-nitrotoluene

A mixture of 5-fluoro-2-nitrotoluene (5.11 g, 32.9 mmol), morpholine (4.31 mL, 49.4 mmol) and K_2CO_3 (6.83 g, 49.4 mmol) was diluted in anhydrous DMSO (80 mL) at room temperature with stirring. The mixture was heated to 80°C for 24 h. After cooling to room temperature, H_2O was added and the resultant mixture was extracted with EtOAc (3X, 50 mL). The organic layer was washed with sat'd aqueous NaCl (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The remaining solid was triturated in heptane (200 mL) and filtered to give the desired material (7.10 g, 97%) as a yellow powder: R_f 0.40 (75% heptane/ 25% ethyl acetate). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.96

(d, J = 9.9 Hz, 1H), 8.85-8.88 (m, 2H), 3.70 (t, J = 5.0 Hz, 4H), 3.35 (t, J = 5.0 Hz, 4H), 2.53 (s, 3H).

Preparation of 5-Morpholinoindole

Under an atmosphere of nitrogen, a solution of 5-morpholinyl-2-nitrotoluene (7.0 g, 31.5 mmol) in DMF (100mL) was treated with dimethylformamide dimethyl acetal (4.81 mL, 36.2 mmol) and pyrrolidine (2.62 mL, 31.5 mL). The mixture was heated to 100°C and maintained for 12 h. After cooling, the mixutre was concentrated *in vacuo* to give the desired intermediate as a brick-red solid.

The intermediate enamine was dissolved in EtOAc (200 mL) and added to a pre-charged Parr bottle with 10% Pd/C (600 mg) in EtOAc (40 mL). The mixture was hydrogentated on a Parr-shaker at 55 psi for 2.5 h. The catalyst was filtered through a Celite plug with several washings with EtOAc and the remaining filtrate concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography (1:1 Hept/EtOAc) to give 2.0 g (31% over 2 steps) of the desired indole as a cream powder: R_f 0.30 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 300 MHz) δ 10.77 (br s, 1H), 7.24 (s, 1H), 7.18-7.20 (m, 1H), 6.97 (d, J = 1.8 Hz, 1H), 6.81 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 6.25 (dd, J_1 = 3.0 Hz, J_2 = 1.8 Hz, 1H), 3.7 (t, J = 4.50 Hz, 4H), 2.96 (t, J = 4.50 Hz, 4H).

Preparation of 5-morpholino-3(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-*N*-acetic acid

5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N- acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 5-morpholinoindole was used instead of 5-chloroindole. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.64-7.72 (m, 1H), 7.34 (s, 1H), 7.26 (d, J = 9.0 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.91 (dd, J_1= 9.0 Hz, J_2= 2.4 Hz, 1H), 4.95 (s, 2H), 4.60 (s, 2H), 3.70-3.73 (m, 4H), 2.97-3.00 (m, 4H); LRMS calcd for $C_{22}H_{18}F_3N_3O_3S$: 461.0; found 462 (M + 1)$^+$. Anal. Calcd for $C_{22}H_{18}F_3N_3O_3S \cdot 1H_2O$: C, 55.11; H, 4.20; N, 8.76; S, 6.69. Found: C, 55.11; H, 4.05; N, 8.57; S, 6.50.

Example 18

Preparation of 6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid

Preparation of 4-Morpholino-2-nitrotoluene

A mixture of 4-fluoro-2-nitrotoluene (15.34 g, 98.9 mmol), morpholine (12.94 mL, 49.4 mmol) and K_2CO_3 (6.83 g, 148.3 mmol) were diluted in anhydrous DMSO (250 mL) at room temperature with stirring. The mixture was heated to 120°C for 24 h. After cooling to room temperature, H_2O was added and the resultant mixture was extracted with EtOAc (3X, 75 mL). The organic layer was washed with sat'd brine (100 mL), dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The remaining solid was triturated in hepatane (200 mL) and filtered to give the desired material (8.00 g, 36.4%) as a yellow powder: R_f 0.40 (25% ethyl acetate in heptane). ^1H NMR (DMSO-d_6, 300 MHz) δ 7.40 (d, J = 2.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.20 (dd, J_1 = 8.7 Hz, J_2 = 2.7 Hz, 1H), 3.70 (t, J = 4.8 Hz, 4H), 3.35 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H).

Preparation of 6-Morpholinoindole

Under an atmosphere of nitrogen, a solution of 4-morpholino-2-nitrotoluene (7.1 g, 31.9 mmol) in DMF (100 mL) was treated with dimethylformamide dimethyl acetal (4.92 mL, 37.1 mmol) and pyrrolidine (2.67 mL, 31.9 mL). The mixture was heated to 100°C and maintained for 12 h. After cooling, the mixture was concentrated *in vacuo* to give the desired intermediate as a brick-red solid. The crude intermediate was dissolved in glacial HOAc (250 mL) and warmed to 85°C. Zn (18.17 g, 0.278 mol) was added to the solution portionwise over 30 min. The mixture was heated for 4h. After cooling to room temperature, the mixture was neutralized with sat'd $NaHCO_3$ and extracted with Et_2O (3X, 300 mL). The combined organics were washed with sat'd brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by SiO_2 flash chromatography (heptane to 2:1 heptane/EtOAc) to give the desired material as

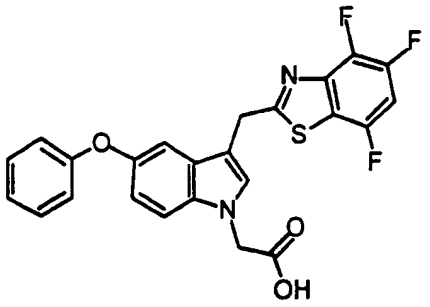
a white crystalline powder (1.0 g, 11% over 2 steps): R_f 0.50 (2:1 Heptane/EtOAc); ^{1}H NMR (DMSO)-d_6, 300 MHz) δ 10.73 (br s, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.80 (s, 1H), 6.73 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 3.72 (t, J = 4.8 Hz, 4H), 3.02 (t, J = 4.8 Hz, 1H).

Preparation of 6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl indole-*N*-acetic acid

6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N-acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 6-morpholinoindole was used instead of 5-chloroindole in step 1: mp 178-180°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.66-7.72 (m, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 7.06 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 4.96 (s, 2H), 4.58 (s, 2H), 3.37-3.75 (m, 4H), 3.09-3.13 (m, 4H); LRMS calcd for $C_{22}H_{18}F_3N_3O_3S$: 461.0; found 462 $(M+1)^+$. Anal. Calcd for $C_{22}H_{18}F_3N_3O_3S$ CH_2Cl_2 0.50H_2O: C, 49.74; H, 3.72; N, 7.57; S, 5.77 Found C, 49.73; H, 3.36; N, 7.69; S, 5.58

Example 19

Preparation of 5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid



5-Phenoxy-2-nitrotoluene

A solution of phenol (12.16 g, 0.129 mol) in anhydrous DMSO was treated with K_2CO_3 (17.88 g, 0.129 mol) and stirred at room temperature for 15 min. 5-Fluoro-2-nitrotoluene (13.38 g, 0.086 mol) was added to the solution *via* syringe. The resultant mixture was heated to 80°C for 12 h. After cooling to room temperature, the mixture was poured into H_2O (100mL). After extraction with EtOAc (2X, 100mL), the organics were combined and washed with a sat'd brine solution, drieds over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (heptane to 8:1 heptane/ EtOAc) to give the desired material as a yellow crystalline solid (12.50 g, 63%): R_f 0.60 (85% heptane/ 15% EtOAc); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.05 (d, J = 9.0 Hz, 1H), 7.44-7.47 (m, 2H), 7.23-7.29 (m, 1H), 7.12-7.16 (m, 2H), 7.04 (d, J = 2.7 Hz, 1H), 6.90 (dd, J_1 = 9.0 Hz, J_2 = 2.7 Hz, 1H), 2.51 (s, 3H).

5-Phenoxyindole

A solution of 5-phenoxy-2-nitrotoluene (10.03 g, 0.0428 mol) in anhydrous DMF was treated with *N,N*-dimethylformamide

dimethyl diacetal (6.73 mL, 0.0508 mol) and pyrrolidine (3.63 mL, 0.0438 mol) and heated to 110 C for 2.5 h. After cooling to room temperature, the mixture was diluted with EtOAc (500 mL) and washed H_2O (500 mL). The organics were dried over MgSO4, filtered and concentrated *in vacuo*. The crude intermediate was dissolved in glacial HOAc (250 mL) and warmed to 85°C. Zn (24.62 g, 0.377 mol) was added to the solution portion wise over 30 min. The mixture was heated for 4h. After cooling to room temperature, the mixture was neutralized with sat'd $NaHCO_3$ and extracted with Et_2O (3X, 300 mL). The combined organics were washed with sat'd brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography (heptane to 2:1 heptane/ EtOAc) to give the desired material as a white crystalline powder (3.1 g, 34% over 2 steps): R_f 0.50 (2:1 Heptane/ EtOAc); ^1H NMR (DMSO-d_6, 300 MHz) δ 11.12 (br s, 1H), 7.48 (s, 1H), 7.30-7.38 (m, 1H), 7.25-7.29 (m, 2H), 7.17 (d, J = 2.7 Hz, 1H), 6.89-7.02 (m, 1H), 6.86-6.88 (m, 2H), 6.80 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 6.37 (m, 1H).

Preparation of 5-phenoxy-3-(4,5,7-triflurobenzothiazol-2-yl)methyl indole-*N*-acetic acid

5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N- acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 5-phenoxyindole was

used instead of 5-chloroindole in step 1: mp 128-130°C; R_f 0.45 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.65-7.70 (m, 1H), 7.47 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.21-7.27 (m, 3H), 6.98 (m, 1H), 6.83-6.90 (m, 3H), 5.02 (s, 2H), 4.60 (s, 2H); LRMS calcd for $C_{24}H_{15}F_3N_2O_3S$: 468.0; found 467.0 $(M - 1)^-$. Anal. Calcd for $C_{24}H_{15}F_3N_2O_3S$: C, 55.11; H, 4.20; N, 8.76; S, 6.69. Found: C, 55.11; H, 4.05; N, 8.57; S, 6.50.

Example 20

Preparation of 7-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

7-Fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N- acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 7-fluoroindole was used instead of 5-chloroindole in step 1: mp 194-196°C; R_f 0.60 (10% methanol in chloroform); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.67-7.73 (m, 1H), 7.46 (s, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 6.89-6.99 (m, 2H), 5.06 (s, 2H), 4.64 (s, 2H); LRMS calcd for $C_{18}H_{10}F_4N_2O_2S \bullet H_2O$: C,50.23; H, 3.28; N, 6.51; S, 7.45. Found C, 50.70; H, 2.52; N, 6.60; S, 7.57. 394.0; found 395.0 $(M + 1)^+$. Anal. Calcd for $C_{18}H_{10}F_4N_2O_2S$

Example 21

Preparation of 7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N- acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 7-bromoindole was used instead of 5-chloroindole in step 1: mp 228-230°C; R_f 0.40 (10% methanol in chloroform); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.65-7.74 (m, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.32 (d, J = 7.8 Hz, 1H), 6.94 (t, J = 7.8 Hz, 1H), 5.29 (s, 2H), 4.65 (s, 2H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SBr$: 454.0 for (^{79}Br and 456.0 for ^{81}Br); found 453.0 $(M - 1)^-$ and 455.0 $(M - 1)^-$. Anal Calcd for $C_{18}H_{10}F_3N_2O_2SBr$: C, 47.49; H, 2.21; N, 6.15; S, 7.04. Found: C, 47.65;H, 2.27; N, 6.15; S, 6.98.

Example 22

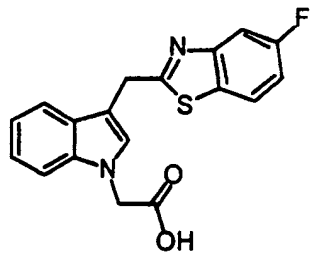
Preparation of 7-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid

7-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl indole-N- acetic acid was prepared in a manner analogous to that set forth in Example 2, except that 7-chloroindole was used instead of 5-chloroindole in step 1: mp 228-230°C; R_f 0.38 (10% methanol in chloroform); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.62-7.73 (m, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.49 (s, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 5.25 (s, 2H), 4.65 (s, 2H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 410.0; found 409.0

(M - 1)⁻. Anal. Calcd for $C_{18}H_{10}F_3N_2O_2SCl$: C, 52.63; H, 2.45; N, 6.82; S, 7.81. Found: C, 52.60; H, 2.54; N, 6.66; S, 7.59.

Example 23

3-[5-Fluorbenzothiazole-2-yl]methyl-indole-*N*-acetic Acid



3-[5-fluorbenzothiazole-2-yl]methyl-indole-*N*-acetic acid was prepared in a manner analogous to that set forth in Example 3, except 2-amino-4-fluorothiophenol hydrochloride was used instead of 2-amino-4,5,7-trifluorothiophenol hydrochloride in step 6: mp 208°C (decomp); R_f0.10 (10% methanol in diehloromethane) ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.91 (s, 1 H), 7.98 (dd, *J* = 8.9, 5.6 Hz: 1 H), 7.78 (dd, *J* = 10.0, 2.6 Hz, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.40 (s, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 7.26 (dt, *J* = 8.9, 2.4 Hz, 1 H), 7.13 (t, *J* = 7.8 Hz, 1 H), 7.01 (t, *J* = 7.8 Hz, 1 H), 5.01 (s, 2 H), 4.56 (s, 2 H); LRMS *m/z* 341.0 (M + 1)⁺, 339.0 (M-1). Anal. Calcd for $C_{18}H_{13}FN_2O_2S$: C, 63.52; H, 3.85; N, 8.23; S, 9.42; Found: C, 63.40; H, 3.80; N, 8.37; S, 9.43.

Example 24

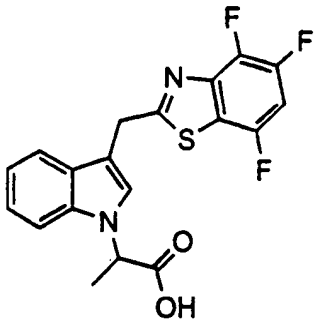
3-[6-Fluorbenzothiazole-2-yl]methyl-indole-*N*-acetic Acid

3-[6-fluorbenzothiazole-2-yl]methyl-indole-*N*-acetic acid was prepared in a manner analogous to that set forth in Example 3, except 2-amino-5-fluorothiophenol hydrochloride was used instead of 2-amino-4,5,7-trifluorothiophenol hydrochloride in step 6: mp 203°C (decomp) R_f0.13 (10% methanol in diehloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.91 (s, 1 H), 7.95 (dd, *J* = 8.9, 5.0 Hz: 1 H), 7.86 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.50 (d, *J* = 7.5 Hz, 1 H), 7.40-7.35 (m, 2 H), 7.32 (dt, *J* = 8.9, 2.7 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.00 (t, *J* = 7.6 Hz, 1 H), 5.01 (s, 2 H), 4.54 (s, 2 H); LRMS *m/z* 341.0 (M + 1)$^+$, 339.0 (M-1. Anal. Calcd for $C_{18}H_{13}FN_2O_2S$: C, 63.52; H, 3.85; N, 8.23; S, 9.42. Found: C, 63.52; H, 3.86; N, 8.35; S, 9.53.

The compounds of Examples 25-32 were prepared essentially according to the procedures set forth above in examples 1and/or 2 with appropriate substitution of starting materials.

Example 25

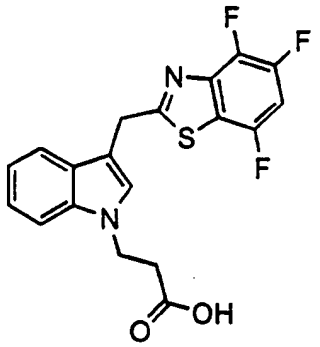
3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-2-propionic acid



mp 176-177°C; R_f 0.34 (20% methanol in dichlormethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.60-7.73 (m, 1H), 7.60 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), t, *J*=7.5 Hz, 1H), 7.02 (t, *J*=7.5 Hz, 1H), 5.35 (q, *J*= 8.1 Hz, 1H), 4.64 (s, 2H), 1.72 (d, *J* = 8.1 Hz, 3H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; Found 391.0 (M * 1)$^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_2SH_2O$: C, 55.88; H, 3.70; N, 6.86; S, 7.85 Found: C, 56.09; H, 3.31; N, 6.89; S, 7.99.

Example 26

3-(4-5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-3-propionic acid



mp 200-201°C; R_f 0.50 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63-7.71 (m, 1H), 7.51 (s, 1H), 7.47 (d,

J = 3.0 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.00 (t, J= 7.5 Hz, 1H), 4.61 (s, 2H), 4.39 (t, J = 6.6 Hz, 2H), 2.75 (t, J = 6.6 Hz, 2H); LRMS calcd for $C_{19}H_{13}F_3N_2O_2S$: 390.0; Found 391.0 (M +1)$^+$. Anal Calcd for $C_{19}H_{13}F_3N_2O_2S$: C, 58.46; H, 3.36; N, 7.18; S, 8.21 Found: C, 58.63; H, 3.40; N, 7.20; S, 8.30.

Example 27

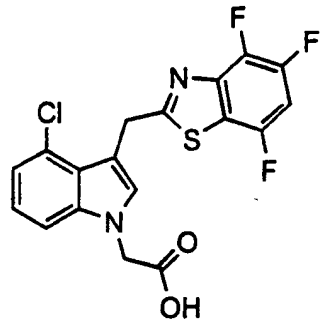
Preparation of 6-Bromo-3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-N-acetic acid: mp 265-267°C; R_f 0.19 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.28 (s, 1H), 8.22 (d, J = 8.7 Hz, 1H), 7.67-7.69 (m, 2H), 7.43-7.47 (m, 2H), 7.14 (d, J = 9.0 Hz, 1H), 5.04 (s, 2H), 4.61 (s, 2H); LRMS calcd for $C_{19}H_{12}F_3N_2O_2SBr$:469.0; Found 469.0 (M + 1)$^+$ for Br = 79. Anal. Calcd for $C_{19}H_{12}F_3N_2O_2SBr$: C, 48.63; H, 2.58; N, 5.97; S, 6.83. Found: C, 48.60; H, 2.63; N, 5.88; S, 6.91.

Example 28

6-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid: mp 118-120°C; R_f 0.27 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63-7.73 (m, 1H), 7.39 (s, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.07 (s, 1H), 6.78 (d, J = 8.7 Hz, 1H), 4.97 (s, 2H), 4.61 (s, 2H); 3.07 (s, 3H); LRMS calcd for $C_{19}H_{13}F_3N_2O_3S$: 406.0; Found 407.0 (M +)$^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_3SH_2O$: C, 53.77; H, 3.56; N, 6.60; S, 7.56 Found: C, 53.87; H, 3.56; N, 6.67; S, 7.67.

Example 29

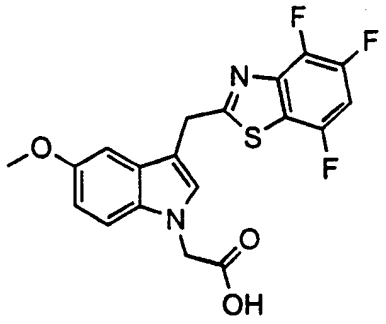
4-Chloro-3-(4,5,7-trifluorobenzothiazol-2yl) methyl-indole-N-acetic acid



mp 203-206 °C; R_f 0.24 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63-7.71 (m, 1H), 7.57 (s, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.12 (dd, $J_{(1)}$= 9.0, $J_{(2)}$= 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 5.08 (s, 2H), 4.78 (s, 2H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SCl$: 410.0; Found 411.0 $(M+1)^+$ and 409.0 $(M-1)^-$.

Example 30

5-Methoxy-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid



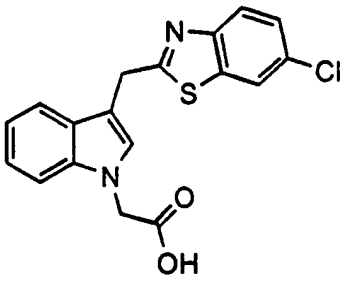
mp 165-167 °C; R_f 0.37 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.61-7.70 (m, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.26 (s, 1H), 6.90 (s, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 4.79 (s, 2H); 4.56 (s, 2H), 3.72 (s, 3H); LRMS calcd for $C_{10}H_{13}F_3N_2O_2S$: 406.0; Found 407.0 $(M+1)^+$ and 405.0 $(M-1)^-$.

Example 31

5-Bromo-3-(4,5,7-trifluorobenzothiazol-2-yl) methyl-indole-N-acetic acid: mp 209-294 °C; R_f 0.18 (20% methanol in dichloromethane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.78 (d, *J* = 1.8 Hz, 1H), 7.65-7.73 (m, 1H), 7.49 (s, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.25 (dd, $J_{(1)}$ = 9.0 Hz, $J_{(2)}$ = 1.8 Hz, 1H), 5.04 (s, 2H); 4.64 (s, 2H); LRMS calcd for $C_{18}H_{10}F_3N_2O_2SBr$: 455.0; Found 455.0 $(M+1)^+$ for Br 79 and 457 $(M+1)^+$ for Br 81.

Example 32

3-(6-chlorobenzothiazol-2-yl) methyl-indole-N-acetic acid



Representative compounds of the invention were tested for their potency, selectivity and efficacy as inhibitors of human aldose reductase. The potency or aldose reductase inhibiting

effects of the compounds were tested using methods similar to those described by Butera et al. in *J. Med. Chem.* **1989**, *32*, 757. Using this assay, the concentrations required to inhibit human aldose reductase (hALR2) activity by 50% (IC50) were determined.

In a second assay, a number of the same compounds were tested for their ability to inhibit aldehyde reductase (hALR1), a structurally related enzyme. The test method employed were essentially those described by Ishii, et al., *J. Med. Chem.* **1996** *39*: 1924. Using this assay, the concentrations required to inhibit human aldehyde reductase activity by 50% (IC50) were determined.

From these data, the hALR1 / hALR2 ratios were determined. Since high potency of test compounds as inhibitors of aldose reductase is desirable, low hALR2 IC50 values are sought. On the other hand, high potency of test compounds as inhibitors of aldehyde reductase is undesirable, and high hALR1 IC50s values are sought. Accordingly, the hALR1 / hALR2 ratio is used to determine the selectivity of the test compounds. The importance of this selectivity is described in Kotani, et al., *J. Med. Chem. 40*: 684, **1997**.

The results of all these tests are combined and illustrated in Table 1.

Example #	hALR2 (IC50)	HALR1 (IC50)	HALR1 / hALR2
1	8 nM	13,000 nM	1,200
2	10nM	11,000nM	1,100
3	5 nM	27,000 nM	5,400
4	8 nM	34,000 nM	4,250
5	6 nM	21,000 nM	3,500
6	8 nM	2,700 nM	340
7	12 nM	4,800 nM	400
8	7 nM	7,500 nM	1,100
9	11 nM	21,000 nM	1,900
10	5nM	13,000 nM	2,600
11	99 nM	5,600 nM	57
12	102 nM	10,000 nM	98
13	73 nM	13,000 nM	178
14	101 nM	16,000	160
15	53 nM	10,000	190
16	25 nM	6,200 nM	248
17	8 nM	41,000 nM	5,100
18	15 nM	>100 μM	>6,700
19	30 nM	11,000 nM	370
20	7 nM	7,000 nM	1,000
21	14 nM	18,000 nM	1,300
22	9.1 nM	19,000 nM	2,100
23	9 nM	6,500 nM	720
24	1,040 nM	4,500 nM	4
25	160 nM	6,500 nM	41
26	17 nM	88,000 nM	5,200
27	52 nM	<5,000 nM	<96
28	5 nM	12,000 nM	2,400
29	11 nM	14,000	1,270
30	7.7 nM	21,000 nM	2,700

31	13 nM	9,700	746
32	660 nM	Not Tested	Not Tested
Tolrestat	13 nM	1,940 nM	149

The results show the superior potency, selectivity and efficacy of representative compounds of the invention. Such compounds are useful in the treatment of chronic complications arising from diabetes mellitus, such as diabetic cataracts, retinopathy and neuropathy. Accordingly, an aspect of the invention is treatment of such complications with the inventive compounds; treatment includes both prevention and alleviation. The compounds are useful in the treatment of, for example, diabetic cataracts, retinopathy, nephropathy and neuropathy.

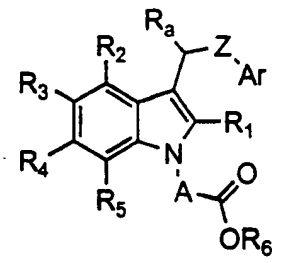
In a third, optional, set of experiments, the compounds can be assayed for their ability to normalize or reduce sorbitol accumulation in the sciatic nerve of streptozotocin-induced diabetic rats. The test methods employed to determine the efficacy are essentially those of Mylari, et al., *J. Med. Chem.* 34: 108, **1991**.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the

present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

We claim:

1. A compound of the formula:



wherein

A is a C_1-C_4 alkylene group optionally substituted with C_1-C_2 alkyl or mono- or disubstituted with halogen;

Z is a bond, O, S, C(O)NH, or C_1-C_3 alkylene optionally substituted with C_1-C_2 alkyl;

R_1 is hydrogen, alkyl having 1-6 carbon atoms, halogen, 2-, 3-, or 4-pyridyl, or phenyl, where the phenyl or pyridyl is optionally substituted with up to three groups selected from halogen, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, nitro, amino, or mono- or di(C_1-C_6)alkylamino;

R_2, R_3, R_4 and R_5 are each independently

hydrogen, halogen, nitro, or an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens);

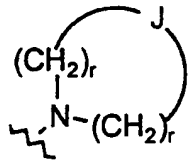
OR_7, SR_7, $S(O)R_7$, $S(O)_2N(R_7)_2$, $C(O)N(R_7)_2$, or $N(R_7)_2$, wherein each R_7 is independently hydrogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups

independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenyl or heteroaryl such as 2-, 3- or 4-imidazolyl or 2-, 3-, or 4-pyridyl, each of which phenyl or heteroaryl is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

phenoxy where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

a group of the formula



where

J is a bond, CH_2, oxygen, or nitrogen; and

each r is independently 2 or 3;

R_6 is hydroxy or a prodrug group;

R_a is hydrogen, C_1-C_6 alkyl, fluoro, or trifluoromethyl;

and Ar represents

a phenyl group optionally substituted with up to 5 groups independently selected from halogen, an alkyl group of 1-6 carbon atoms (which may be substituted with one or more halogens), nitro, OR_7, SR_7, $S(O)R_7$, $S(O)_2R_7$ or $N(R_7)_2$ wherein R_7 is hydrogen, an alkyl group of 1-6 carbon atoms (which

may be substituted with one or more halogens) or benzyl, where the phenyl portion is optionally substituted with up to three groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, or the phenyl group may be condensed with benzo where the benzo is optionally substituted with one or two of halogen, cyano, nitro, trifluoromethyl, perfluoroethyl, trifluoroacetyl, or (C_1-C_6)alkanoyl, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, trifluoromethoxy, trifluoromethylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl;

a heterocyclic 5-membered ring having one nitrogen, oxygen or sulfur, two nitrogens one of which may be replaced by oxygen or sulfur, or three nitrogens one of which may be replaced by oxygen or sulfur, said heterocyclic 5-membered ring substituted by one or two fluoro, chloro, (C_1-C_6)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thienyl, said phenyl or benzo optionally substituted by one of iodo, cyano, nitro, perfluoroethyl, trifluoroacetyl, or (C_1-C_6)alkanoyl, one or two of fluoro, chloro, bromo, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, trifluoromethoxy, trifluoromethylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl or trifluoromethyl, or two fluoro or two trifluoromethyl with one hydroxy or

one (C_1-C_6)alkoxy, or one or, preferably, two fluoro and one trifluoromethyl, or three fluoro, said pyridyl, furyl or thienyl optionally substituted in the 3-position by fluoro, chloro, bromo, (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

a heterocyclic 6-membered ring having one to three nitrogen atoms, or one or two nitrogen atoms and one oxygen or sulfur, said heterocyclic 6-membered ring substituted by one or two (C_1-C_6)alkyl or phenyl, or condensed with benzo, or substituted by one of pyridyl, furyl or thienyl, said phenyl or benzo optionally substituted by one of iodo or trifluoromethylthio, or one or two of fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, or trifluoromethyl, and said pyridyl, furyl or thienyl optionally substituted in the 3-position by fluoro, chloro, (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

said benzo-condensed heterocyclic 5-membered or 6-membered rings optionally substituted in the heterocyclic 5-membered or 6-membered ring by one of fluoro, chloro, bromo, methoxy, or trifluoromethyl;

oxazole or thiazole condensed with a 6-membered aromatic group containing one or two nitrogen atoms, with thiophene or with furane, each optionally substituted by one of fluoro, chloro, bromo, trifluoromethyl, methylthio or methylsulfinyl;

imidazolopyridine or triazolopyridine optionally substituted by one of trifluoromethyl, trifluoromethylthio, bromo, or (C_1-C_6)alkoxy, or two of fluoro or chloro;

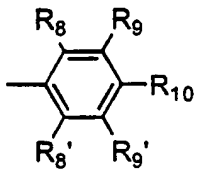
thienothiophene or thienofuran optionally substituted by one of fluoro, chloro or trifluoromethyl;

thienotriazole optionally substituted by one of chloro or trifluoromethyl;

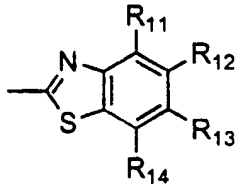
naphthothiazole; naphthoxazole; or thienoisothiazole.

2. A compound according to claim 1, wherein Ar is aryl or heteroaryl, each of which is substituted with up to four groups independently selected from hydrogen, fluorine, chlorine, bromine, trifluoromethyl and nitro.

3. A compound according to claim 1, wherein Ar is a substituted phenyl of Formula II or a substituted benzothiazole of Formula III



II



III

wherein R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are independently hydrogen, fluorine, chlorine, bromine, trifluoromethyl or nitro.

4. A compound according to claim 3, wherein A is methylene and Z is a bond.

5. A compound according to claim 3, wherein R_a is hydrogen and Z is a bond.

6. A compound according to claim 3, wherein A is methylene, R_a is hydrogen, and Z is a bond.

7. A compound according to claim 6, wherein Ar is a substituted benzothiazole of Formula III.

8. A compound according to claim 7, wherein at least one of R_{11}, R_{12}, R_{13}, and R_{14} is trifluoromethyl.

9. A compound according to claim 8, wherein R_{12} is trifluoromethyl.

10. A compound according to claim 7, wherein R_{11}, R_{12}, and R_{14} are fluorines and R_{13} is hydrogen.

11. A compound according to claim 10, wherein R_6 is hydrogen.

12. A compound according to claim 10, wherein R_6 is C_1-C_6 alkyl.

13. A compound according to claim 6, wherein Ar is a substituted phenyl of Formula II.

14. A compound according to claim 13, wherein at least one of R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10} is trifluoromethyl.

15. A compound according to claim 14, wherein R_9 is trifluoromethyl.

16. A compound according to claim 15, wherein R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10} are fluorines and R_{13} is hydrogen.

17. A compound according to claim 16, wherein R_6 is hydrogen.

18. A compound according to claim 16, wherein R_6 is C_1-C_6 alkyl.

19. A compound according to claim 1, which is 3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid, ethyl Ester.

20. A compound according to claim 1, which is 3-(4,5,7-trifluorobenzothiazol-2yl) methyl-indole-*N*-acetic acid.

21. A compound according to claim 1, which is 5-chloro-3-(4,5,7-Trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

22. A compound according to claim 1, which is 5-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

23. A compound according to claim 1, which is 2-methyl-3-(4,5,7 trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

24. A compound according to claim 1, which is 5-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

25. A compound according to claim 1, which is 7-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

26. A compound according to claim 1, which is 6-chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

27. A compound according to claim 1, which is 5-benzyloxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

28. A compound according to claim 1, which is 6-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

29. A compound according to claim 1, which is 5-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

30. A compound according to claim 1, which is 6-methyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

31. A compound according to claim 1, which is 3-(5-trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

32. A compound according to claim 1, which is 5-Methyl-3-(5-Trifluoromethylbenzothiazol-2-yl)methyl-indole-*N*-acetic acid.

33. A compound according to claim 1, which is 3-(3-nitrophenyl)methyl-indole-*N*-acetic acid.

34. A compound according to claim 1, which is 3-(3-nitrophenyl)methyl-indole-*N*-acetic acid, ethyl ester.

35. A compound according to claim 1, which is 3-(3-nitrophenyl)methyl-indole-*N*-acetic acid.

36. A compound according to claim 1, which is 2-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

37. A compound according to claim 1, which is 5-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

38. A compound according to claim 1, which is 6-phenyl-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

39. A compound according to claim 1, which is 5-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

40. A compound according to claim 1, which is 6-morpholino-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

41. A compound according to claim 1, which is 5-phenoxy-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

42. A compound according to claim 1, which is 7-fluoro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

43. A compound according to claim 1, which is 7-bromo-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

44. A compound according to claim 1, which is -chloro-3-(4,5,7-trifluorobenzothiazol-2-yl)methyl-indole-N-acetic acid.

45. A compound according to claim 1, which is 3-[[5-Fluorbenzothiazole-2-yl]methyl]-indole-*N*-acetic acid.

46. A compound according to claim 1, which is 3-[[6-Fluorbenzothiazole-2-yl]methyl]-indole-*N*-acetic acid.

47. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1.

48. A method of preventing or alleviating chronic complications arising from diabetes mellitus, which comprises administering to a mammal in need of such treatment an effective amount of a compound according to claim 1.

49. A method according to claim 37 wherein the complications are selected from the group consisting of diabetic cataracts, retinopathy, nephropathy and neuropathy.

50. A compound according to claim 3, wherein Ar is a substituted benzothiazole of Formula III, R_{12} is trifluoromethyl, A is methylene, methylene substituted with a methyl group, or ethylene, and R_2, R_3, R_4 and R_5, in combination, represent one of bromo, cyano or nitro, one or two of fluoro, chloro, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or trifluoromethyl, or two fluoro or two methyl with one hydroxy or one (C_1-C_6)alkoxy, or one or, preferably, two fluoro and one methyl, or three fluoro groups.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 417/06, 209/10, A61K 31/405 //
(C07D 417/06, 277:00, 209:00)

A3

(11) International Publication Number: WO 99/50268

(43) International Publication Date: 7 October 1999 (07.10.99)

(21) International Application Number: PCT/US99/07116

(22) International Filing Date: 31 March 1999 (31.03.99)

(30) Priority Data:
60/080,143 31 March 1998 (31.03.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/080,143 (CIP)
Filed on 31 March 1998 (31.03.98)

(71) Applicant *(for all designated States except US)*: THE INSTITUTES FOR PHARMACEUTICAL DISCOVERY, INC. [US/US]; 23 Business Park Drive, Branford, CT 06405 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: JONES, Michael, L. [US/US]; 3710 Stoney Creek Road, Chapel Hill, NC 27514 (US). GUNN, David [US/US]; 40 Wood Street, Hamden, CT 06517 (US). JONES, John, Howard [US/US]; 3893 Main Street, Stratford, CT 06497 (US). VAN ZANDT, Michael, C. [US/US]; 56 Barker Hill Drive, Guilford, CT 06437 (US).

(74) Agent: SARUSSI, Steven, J.; McDonnell Boehnen Hulbert & Berghoff, Suite 3200, 300 South Wacker Drive, Chicago, IL 60606 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
16 December 1999 (16.12.99)

(54) Title: SUBSTITUTED INDOLEALKANOIC ACIDS

(57) Abstract

Disclosed are substituted indolealkanoic acids useful in the treatment of chronic complications arising from diabetes mellitus. Also disclosed are pharmaceutical compositions containing the compounds and methods of treatment employing the compounds, as well as methods for their synthesis.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 99/07116

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/06 C07D209/10 A61K31/405 //(C07D417/06,277:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 054 417 A (PFIZER LTD ;PFIZER (PA)) 23 June 1982 (1982-06-23) abstract ---	1,47
X	WO 95 06046 A (PFIZER LTD ;PFIZER RES & DEV (IE); PFIZER (US); CROSS PETER EDWARD) 2 March 1995 (1995-03-02) page 50, prep.16; page 52, prep.17,18; page 53, prep.19; page 63, prep.31 ---	1
X	WO 96 03376 A (LILLY CO ELI ;BACH NICHOLAS J (US); DILLARD ROBERT D (US); DRAHEIM) 8 February 1996 (1996-02-08) example 1, parts F,G; example 2, parts D,E --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1999	04/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 99/07116

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 330 997 A (MYLARI BANAVARA L ET AL) 19 July 1994 (1994-07-19) cited in the application the whole document	1-47,50
Y	WO 93 12786 A (HOWARD HARRY R JR ;SARGES REINHARD (US)) 8 July 1993 (1993-07-08) the whole document; compounds I,III	1-47,50
A	EP 0 222 576 A (PFIZER) 20 May 1987 (1987-05-20) the whole document	1-47,50
A	FR 2 647 676 A (UNION PHARMA SCIENT APPL) 7 December 1990 (1990-12-07) the whole document	1-47,50
A	EP 0 401 981 A (PFIZER) 12 December 1990 (1990-12-12) the whole document	1-47,50
A	EP 0 714 893 A (GRELAN PHARMACEUTICAL CO) 5 June 1996 (1996-06-05) cited in the application the whole document	1-47,50
A	WO 96 26207 A (NISSAN CHEMICAL IND LTD ;OHARA YOSHIO (JP); SUZUKI MIKIO (JP); OHD) 29 August 1996 (1996-08-29) abstract	1-47,50
X	C.W. WHITEHEAD ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 17, no. 12, 1974, pages 1298-1304, XP002118784 WASHINGTON US example 51	1,47
X	R.P. DICKINSON ET AL.: BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 14, 1996, pages 1691-1696, XP004134923 examples 1,7	1,47

2

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US 99/07116

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 48 and 49 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 07116

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-18,47,50 relate to a very large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations open by terms like "a prodrug group" which lacks clarity and conciseness within the meaning of Article 6 PCT that a meaningful search of the claims is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely taking into account the definition of the disputed term given on page 18-19 of the description.
It is furthermore indicated that the definition of the group R6 is misleading since it would said that peroxide derivatives are claimed in contradiction with, for instance, dependent claims 11, 12, 17 and 18. On the basis of the description and the examples the search has been conducted for acidic derivatives and their "prodrugs" as defined in the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/US 99/07116

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0054417 A	23-06-1982	AR 229110 A	15-06-1983
		AU 525296 B	28-10-1982
		AU 7848881 A	24-06-1982
		CA 1143737 A	29-03-1983
		CS 228527 B	14-05-1984
		DD 202290 A	07-09-1983
		DK 552581 A	16-06-1982
		ES 507960 A	01-10-1983
		FI 814003 A	16-06-1982
		GR 76355 A	06-08-1984
		IE 51949 B	29-04-1987
		JP 57181082 A	08-11-1982
		PH 17576 A	01-10-1984
		PT 74123 A,B	01-01-1982
		US 4363912 A	14-12-1982
		YU 293481 A	31-10-1984
		ZA 8108665 A	27-10-1982
WO 9506046 A	02-03-1995	AT 170856 T	15-09-1998
		CA 2170279 A	02-03-1995
		DE 69413238 D	15-10-1998
		DE 69413238 T	28-01-1999
		EP 0715627 A	12-06-1996
		ES 2121223 T	16-11-1998
		FI 960840 A	23-02-1996
		JP 2763962 B	11-06-1998
		JP 8509003 T	24-09-1996
		US 5744488 A	28-04-1998
WO 9603376 A	08-02-1996	AU 3140695 A	22-02-1996
		CA 2195569 A	08-02-1996
		EP 0772592 A	14-05-1997
		JP 10503208 T	24-03-1998
		US 5641800 A	24-06-1997
US 5330997 A	19-07-1994	US 5236945 A	17-08-1993
WO 9312786 A	08-07-1993	AT 56435 T	15-09-1990
		DK 355287 A	08-04-1988
		EP 0252713 A	13-01-1988
		GR 3000854 T	15-11-1991
		IE 59995 B	18-05-1994
		JP 1915546 C	23-03-1995
		JP 6043393 B	08-06-1994
		JP 63023863 A	01-02-1988
		PT 85294 A,B	01-08-1987
EP 0222576 A	20-05-1987	US 4723010 A	02-02-1988
		AT 73801 T	15-04-1992
		AU 574589 B	07-07-1988
		AU 6485886 A	11-06-1987
		CA 1299178 A	21-04-1992
		CN 1009831 B	03-10-1990
		DD 254001 A	10-02-1988
		DE 3684410 A	23-04-1992
		DK 529886 A	08-05-1987
		EG 18144 A	30-08-1992
		FI 864512 A,B,	08-05-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07116

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0222576 A		GR 3004099 T	31-03-1993
		IE 59315 B	09-02-1994
		JP 1715495 C	27-11-1992
		JP 4001747 B	14-01-1992
		JP 62114988 A	26-05-1987
		NZ 218192 A	29-08-1989
		PH 26741 A	28-09-1992
		PT 83684 A,B	01-12-1986
		SU 1551246 A	15-03-1990
		US 4939140 A	03-07-1990
		YU 189086 A	30-06-1988
		CA 1293726 A	31-12-1991
		CA 1290768 A	15-10-1991
		PH 24183 A	22-03-1990
		US 4748280 A	31-05-1988
FR 2647676 A	07-12-1990	NONE	
EP 0401981 A	12-12-1990	US 4996204 A	26-02-1991
		AT 121743 T	15-05-1995
		AU 611610 B	13-06-1991
		AU 5490590 A	15-11-1990
		CA 2016326 A,C	11-11-1990
		DE 69018876 D	01-06-1995
		DE 69018876 T	24-08-1995
		DK 401981 T	04-09-1995
		ES 2071016 T	16-06-1995
		FI 93013 B	31-10-1994
		IE 66029 B	29-11-1995
		IL 94302 A	25-01-1994
		JP 1904155 C	08-02-1995
		JP 3005481 A	11-01-1991
		JP 6031235 B	27-04-1994
		NO 173938 C	23-02-1994
		PT 93984 A,B	08-01-1991
EP 0714893 A	05-06-1996	CA 2163950 A	30-05-1996
		DE 69505484 D	26-11-1998
		DE 69505484 T	12-05-1999
		JP 8208631 A	13-08-1996
		US 5700819 A	23-12-1997
WO 9626207 A	29-08-1996	AU 4731196 A	11-09-1996
		JP 9235284 A	09-09-1997
		ZA 9601478 A	28-08-1996

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☑ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☑ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.